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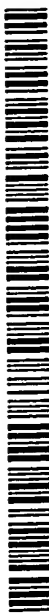
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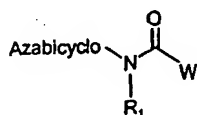
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(54) Title: FUSED BICYCLIC-N-BRIDGED-HETEROAROMATIC CARBOXAMIDES FOR THE TREATMENT OF DISEASE



(I)

(57) Abstract: The invention provides compounds of Formula (I). These compounds may be in the form of pharmaceutical salts or compositions, may be in pure enantiomeric form or racemic mixtures, and are useful in pharmaceuticals to treat conditions or diseases in which  $\alpha_7$  is known to be involved.

## FUSED BICYCLIC-N-BRIDGED-HETEROAROMATIC CARBOXAMIDES FOR THE TREATMENT OF DISEASE

### FIELD OF INVENTION

5           Nicotinic acetylcholine receptors (nAChRs) play a large role in central nervous system (CNS) activity. Particularly, they are known to be involved in cognition, learning, mood, emotion, and neuroprotection. There are several types of nicotinic acetylcholine receptors, and each one appears to have a different role in regulating CNS function. Nicotine affects all such receptors, and has a variety of activities.

10           Unfortunately, not all of the activities are desirable. In fact, one of the least desirable properties of nicotine is its addictive nature and the low ratio between efficacy and safety. The present invention relates to molecules that have a greater effect upon the  $\alpha 7$  nAChRs as compared to other closely related members of this large ligand-gated receptor family. Thus, the invention provides compounds that are active drug

15           molecules with fewer side effects.

          The invention also concerns the synthesis of and isolation of intermediates and final compounds. Specifically, the present invention concerns the stereospecific synthesis of (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or salts thereof.

### 20    BACKGROUND OF THE INVENTION

          Cell surface receptors are, in general, excellent and validated drug targets. nAChRs comprise a large family of ligand-gated ion channels that control neuronal activity and brain function. These receptors have a pentameric structure. In mammals, this gene family is composed of nine alpha and four beta subunits that co-

25           assemble to form multiple subtypes of receptors that have a distinctive pharmacology. Acetylcholine is the endogenous regulator of all of the subtypes, while nicotine non-selectively activates all nAChRs.

          The  $\alpha 7$  nAChR is one receptor system that has proved to be a difficult target for testing. Native  $\alpha 7$  nAChR is not routinely able to be stably expressed in most

30           mammalian cell lines (Cooper and Millar, *J. Neurochem.*, 1997, 68(5):2140-51). Another feature that makes functional assays of  $\alpha 7$  nAChR challenging is that the receptor is rapidly (100 milliseconds) inactivated. This rapid inactivation greatly limits the functional assays that can be used to measure channel activity.

Recently, Eisele et al. has indicated that a chimeric receptor formed between the N-terminal ligand binding domain of the  $\alpha 7$  nAChR (Eisele et al., *Nature*, 366(6454), p 479-83, 1993), and the pore forming C-terminal domain of the 5-HT<sub>3</sub> receptor expressed well in *Xenopus* oocytes while retaining nicotinic agonist sensitivity. Eisele et al. used the N-terminus of the avian (chick) form of the  $\alpha 7$  nAChR receptor and the C-terminus of the mouse form of the 5-HT<sub>3</sub> gene. However, under physiological conditions the  $\alpha 7$  nAChR is a calcium channel while the 5-HT<sub>3</sub>R is a sodium and potassium channel. Indeed, Eisele et al. teaches that the chicken  $\alpha 7$  nAChR/ mouse 5-HT<sub>3</sub>R behaves quite differently than the native  $\alpha 7$  nAChR with the pore element not conducting calcium but actually being blocked by calcium ions. WO 00/73431 A2 reports on assay conditions under which the 5-HT<sub>3</sub>R can be made to conduct calcium. This assay may be used to screen for agonist activity at this receptor.

WO 00/73431 A2 discloses two binding assays to directly measure the affinity and selectivity of compounds at the  $\alpha 7$  nAChR and the 5-HT<sub>3</sub>R. The combined use of these functional and binding assays may be used to identify compounds that are selective agonists of the  $\alpha 7$  nAChR.

US Patent 5,977,144 discloses compositions for benzylidene- and cinnamylidene-anabaseines and methods for using these compositions for treating conditions associated with defects or malfunctioning of nicotinic subtypes brain receptors. These compositions target the  $\alpha 7$  receptor subtype with little or no activation of the  $\alpha 4\beta 2$  or other receptor subtypes.

US Patent 5,599,937 discloses heteroaromatic quinuclidines used for treating diseases related to muscarinic receptor function.

US Patent 5,561,149 discloses the use of a mono or bicyclic carbocyclic, or heterocyclic carboxylic acid, ester or amide or an imidazolyl carbazol in the manufacture of a medicament suitable for the treatment of stress-related psychiatric disorders, for increasing vigilance, for the treatment of rhinitis or serotonin-induced disorders and/or coadministration with another active agent to increase the bioavailability thereof, or for nasal administration.

US Patent 5,543,426 discloses the use of certain 3,7-disubstituted indole compounds for treating depression or cognitive disorders.

US Patent 5,434,161 discloses imidazopyridines as serotonergic 5-HT<sub>3</sub> antagonists.

US Patent 5,362,740 discloses dihydrobenzofuran carboxamides useful in treating CNS disorders, but motility disorders, and/or emesis and/or pain in mammals, and/or migraine.

US Patent 5,342,845 discloses indole derivatives and drugs. The compound of the invention is disclosed as being effective as a gastrointestinal motor activity regulator, antimigraine, antipsychotic or antianxiety drug and for dementia or orthostatic hypotension.

US Patent 5,322,951 discloses certain 1-(2,3-dihydro-indole)carbonyl intermediates useful for preparing 1-(2,3-dihydro)-1-carboxamide final products that possess 5-HT M-receptor antagonist activity.

US 5,183,822 discloses substituted 3,4-Annulated Benzimidazole-2(1H)-ones as being active as 5-HT receptor antagonists.

US 5,063,231 discloses a method of treatment of visceral pain.

US Patent 5,039,680 discloses 5-HT<sub>3</sub> antagonists in preventing or reducing dependency on dependency-inducing agents.

US Patent 5,001,133 discloses substituted benzoic acid heterocyclic amides and esters as being serotonin M antagonists.

US Patent 4,985,437 discloses the use of certain compounds which act as antagonists of 5-hydroxytryptamine (5-HT) at 5-HT<sub>3</sub> receptors for the treatment of cognitive disorders such as attentional and memory deficits and dementia states.

US Patent 4,983,600 discloses heterocyclic compounds useful as 5-HT<sub>3</sub> antagonists.

US Patent 4,973,594 discloses the use of compounds which act as antagonists of 5-hydroxytryptamine (5-HT) at 5-HT<sub>3</sub> receptors for the treatment of depression.

US Patent 4,937,247 discloses 1-acyl indazoles that are disclosed as having 5-HT<sub>3</sub> antagonist activity.

US Patent 4,935,511 discloses benzoxazine and benzoxazepin carboxamide 5-HT<sub>3</sub> antagonists properties including CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D<sub>2</sub> receptor binding affinity.

US 4,933,445 discloses heteroazabenzobicyclic carboxamide 5-HT<sub>3</sub> antagonists.



US Patent 4,921,982 discloses 5-halo-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acids which are useful as intermediates for 5-HT<sub>3</sub> antagonists.

US Patent 4,920,219 discloses substituted saturated and unsaturated indole quinoline and benzazepine carboxamides and their valuable use as 5-HT<sub>3</sub> antagonists having CNS and gastric prokinetic activity void of any significant D<sub>2</sub> receptor binding properties.

US Patent 4,920,127 discloses substituted indoles and their use as 5-HT<sub>3</sub> receptor antagonists.

US Patent 4,910,193 discloses treatment of gastrointestinal disorders.

US Patent 4,882,327 discloses certain heterocyclic N-substituted carboxamides having 5-HT<sub>3</sub> receptor antagonist activity.

US 4,863,919 discloses a method of enhancing memory or correcting memory deficiency with arylamido(and arylthioamido)-azabicycloalkanes.

US Patent 4,835,162 discloses agonists and antagonists to nicotine as smoking deterrents.

US Patent 4,822,795 discloses pharmaceutically useful esters and amides.

US Patent 4,803,199 discloses pharmaceutically useful heterocyclic acid esters and amides or alkylene bridged piperidines as serotonin M antagonists.

US Patent 4,798,829 discloses 1-azabicyclo[3.2.2]nonane derivatives having gastric motility enhancing activity and/or anti-emetic activity and/or 5-HT receptor antagonist activity.

US Patent 4,797,406 discloses amides and esters containing bridged piperidines and use as serotonin M antagonists.

US Patent 4,721,720 discloses a method of treating emesis, anxiety and/or irritable bowel syndrome.

US Patent 4,612,319 discloses bridged quinolizinidinylamides, compositions containing them and methods for their use.

WO 01/76576 A2 discloses a pharmaceutical composition for treatment of acute, chronic pain and/or neuropathic pain and migraines.

WO 01/60821 A1 discloses novel biarylcarboxamides and their use in therapy, especially in the treatment of prophylaxis of psychotic and intellectual impairment conditions.

WO 01/36417 A1 discloses novel N-azabicyclo-amide derivatives and use in therapy, especially in the treatment of prophylaxis of psychotic disorders and intellectual impairment disorders.

WO 99/20633 discloses benzoazine derivatives having an antagonist activity  
5 for 5-HT<sub>3</sub>/5-HT<sub>4</sub> receptors.

WO 97/35860 discloses novel benzimidazol derivatives having an affinity for the serotonergic 5-HT<sub>3</sub>/5-HT<sub>4</sub> receptors.

WO 95/27490 discloses serotonin antagonists (5-HT<sub>3</sub>) for treating fibromyalgia.

10 WO 95/04742 discloses tropyl 7-azaindol-3-ylcarboxyamides as antitussive agents.

WO 93/06108 discloses pyrrolobenzoxazine derivatives as 5-HT agonists and antagonists.

WO 91/17161 discloses isoquinoline amides and esters as 5-HT<sub>3</sub> receptor  
15 antagonists.

WO 91/09593 discloses 5-HT<sub>3</sub> antagonists for treatment of nausea, bradycardia or hypotension associated myocardial instability.

WO 90/14347 A as abstracted in chemical abstract 1991:143,158 discloses N-quinuclidinyl-indolecarboxamide derivatives as being antiemetics.

20 EP 512 350 A2 discloses 3-(indolyl-2-carboxamido) quinuclidines useful for treating diseases characterized by an excess or enhanced sensitivity to serotonin, e.g., psychosis, nausea, vomiting, dementia or other cognitive diseases, migraine, diabetes. The compound may be used to control anxiety, aggression, depression, and pain. The compounds are disclosed as serotonin 5-HT<sub>3</sub> antagonists.

25 EP 483 836 A1 discloses pyrazolo[1,5-a]pyridine-3-carboxylic acid derivatives, their preparation process, and serotonin receptor antagonists containing them as active ingredients.

DE 3810552 A1 discloses esters and amides of indolyl-, benzo[b]thiophenyl-, benzo[b]furancarboxylic acids or 4-amino-2 methoxy-benzoic acids with N-  
30 heterocyclic or N-heterobicyclic alcohols or amines. The compounds disclosed have activity against pain especially migraine, as an anti-arrhythmic for gastrointestinal disturbances, stomach disturbances, gastritis ulcer, gall bladder, spastic colon, Crohn's disease, ulcerative colitis, carcinoid syndrome, diarrhea of various types. The

compounds are also disclosed as speeding stomach emptying, controlling gastro duodenal and gastro esophageal reflux, disturbances of esophageal motility, hiatal hernia, cardiac insufficiency, hypotonic stomach, paralytic ileus, manic depressive psychosis and other psychoses. The compounds are also disclosed as useful for stress related diseases, senility, and enhancement of nasal absorption of other agents, e.g., in the treatment of emesis.

In *Bioorg. & Med. Chem. Lett.* 11 (2001) 319-321, the 5-HT<sub>3</sub> antagonist tropisetron (ICS 205-930) is discussed as a potent and selective  $\alpha 7$  nicotinic receptor partial agonist.

In *Behavioral Brain Res.*, 113 (2000) 169-181, it is discussed that the brain  $\alpha 7$  nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease using DMXBA which is known as GTS-21.

In *Bioorg. & Med. Chem. Lett.* 9 (1999) 1895-1900, it is discussed the discovery of a highly potent, functionally-selective muscarinic M<sub>1</sub> agonist.

In *Bioorg. & Med. Chem. Lett.* 4 (1994) 695-698, it is discussed pyrazolo[1,5-a]pyridines and pyrazolo[1,5-b]pyridazines as 5-HT<sub>3</sub> antagonists.

In *Eur. J. Med. Chem.*, 34 (1999) 415-422, benzimidazole-2-carboxylic acid amides and esters are discussed as a new structural class of 5-HT<sub>3</sub> ligands.

## SUMMARY OF THE INVENTION

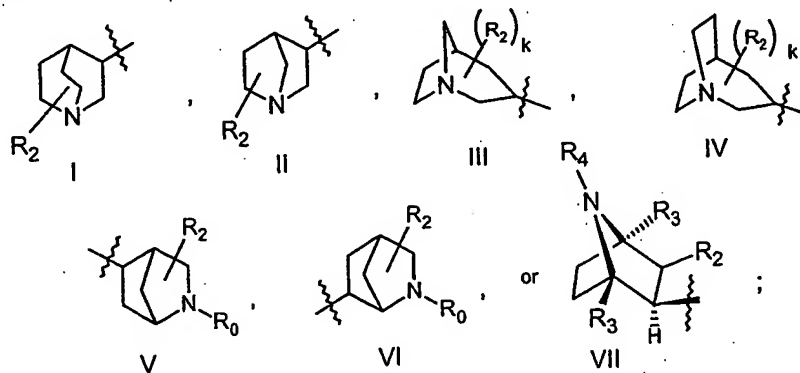
The present invention discloses compounds of the Formula I:



Formula I

wherein R<sub>1</sub> is H, alkyl, or haloalkyl;

Azabicyclo is



R<sub>0</sub> is H, lower alkyl, lower substituted alkyl, or lower halogenated alkyl;

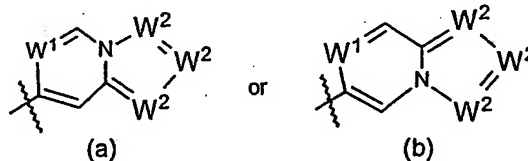
$R_2$  is H, F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

$k$  is 1 or 2, provided that when  $k$  is 2, one  $R_2$  is other than H;

Each  $R_3$  is independently H, alkyl, or substituted alkyl;

5  $R_4$  is H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, -OH, -CN, -NH<sub>2</sub>, -NH(alkyl), or -N(alkyl)<sub>2</sub>;

W is



wherein  $W^1$  is N or CH;

10 Each  $W^2$  is N or C( $R_5$ ), provided that no more than one  $W^2$  is N;

Each  $R_5$  is independently H, alkyl, substituted alkyl, halogenated alkyl, alkenyl, substituted alkenyl, halogenated alkenyl, alkynyl, substituted alkynyl, halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N( $R_{10}$ )<sub>2</sub>, -N( $R_{10}$ )<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, aryl,  $R_7$ ,  $R_9$ , or two  $R_5$  on adjacent carbon atoms may combine for W to be a 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with 1-2 substituents independently selected from F, Cl, Br, I, and  $R_6$ ;

$R_6$  is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -NR<sub>8</sub>R<sub>8</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N( $R_8$ )C(O)NR<sub>8</sub>R<sub>8</sub>, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, phenyl, phenyl having 0-4 substituents independently selected from F, Cl, Br, I and  $R_{15}$ , naphthyl, or naphthyl having 0-4 substituents independently selected from F, Cl, Br, I, or  $R_{15}$ ;

$R_7$  is 5-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms independently selected from the group consisting of -O-, =N-, -N( $R_{14}$ )-, and -S-, and having 0-1 substituent selected from  $R_{15}$ , and further having 0-3 substituents independently selected from F, Cl, Br, or I, wherein the  $R_7$  moiety attaches to other substituents as defined in formula I at any position as valency allows;

Each  $R_8$  is independently H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or  $R_{15}$ ;

5  $R_9$  is 6-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms selected from =N- and having 0-1 substituent selected from  $R_{15}$  and 0-3 substituent(s) independently selected from F, Cl, Br, or I, wherein the  $R_9$  moiety attaches to other substituents as defined in formula I at any position as valency allows;

10 Each  $R_{10}$  is independently H, alkyl, cycloalkyl, heterocycloalkyl, alkyl substituted with 1 substituent selected from  $R_{13}$ , cycloalkyl substituted with 1 substituent selected from  $R_{13}$ , heterocycloalkyl substituted with 1 substituent selected from  $R_{13}$ , halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, phenyl, or substituted phenyl;

15 Each  $R_{11}$  is independently H, alkyl, cycloalkyl, heterocyclo-alkyl, halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

$R_{12}$  is -OR<sub>11</sub>, -SR<sub>11</sub>, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, -NR<sub>11</sub>R<sub>11</sub>, -C(O)R<sub>11</sub>, -NO<sub>2</sub>, -C(O)NR<sub>11</sub>R<sub>11</sub>,  
20 -CN, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>NR<sub>11</sub>R<sub>11</sub>, or -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>;

$R_{13}$  is -OR<sub>11</sub>, -SR<sub>11</sub>, -NR<sub>11</sub>R<sub>11</sub>, -C(O)R<sub>11</sub>, -SOR<sub>11</sub>, -SO<sub>2</sub>R<sub>11</sub>, -C(O)NR<sub>11</sub>R<sub>11</sub>, -CN, -CF<sub>3</sub>, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>NR<sub>11</sub>R<sub>11</sub>, -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>, or -NO<sub>2</sub>;

$R_{14}$  is independently H, alkyl, halogenated alkyl, limited substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, or substituted heterocycloalkyl;

25  $R_{15}$  is alkyl, substituted alkyl, halogenated alkyl, -OR<sub>11</sub>, -CN, -NO<sub>2</sub>, -NR<sub>10</sub>R<sub>10</sub>;

$R_{16}$  is H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, phenyl, or phenyl having 0-4 substituents independently selected from F, Cl, Br, I, and  $R_{15}$ ;

30 or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof.

Embodiments of the invention may include one or more or combination of the following.

One embodiment of the present invention provides a method for using a compound according to Formula I or pharmaceutically acceptable salt thereof for treating, or use of a compound according to Formula I or pharmaceutically acceptable salt thereof for the preparation of a medicament for treating, a disease or condition, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of  $\alpha 7$  nicotinic acetylcholine receptor agonist.

The present invention also includes a method for using a compound according to Formula I or pharmaceutically acceptable salt thereof for treating, or use of a compound according to Formula I or pharmaceutically acceptable salt thereof for the preparation of a medicament for treating, a disease or condition, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of  $\alpha 7$  nicotinic acetylcholine receptor agonist, wherein the disease, or condition is any one or more or combination of the following: cognitive and attention deficit symptoms of Alzheimer's Disease, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia, psychosis, attention deficit disorder, attention deficit hyperactivity disorder, depression, anxiety, general anxiety disorder, post traumatic stress disorder, mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems in general and associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

In another aspect, the invention includes treating a mammal suffering from schizophrenia or psychosis by administering compounds of Formula I in conjunction with antipsychotic drugs (also called anti-psychotic agents). The compounds of the present invention and the antipsychotic drugs can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of the present invention and the antipsychotic drugs can be incorporated into a single pharmaceutical composition. Alternatively, at least two separate compositions, i.e.,

one containing compounds of the present invention and the other containing antipsychotic drugs, can be administered simultaneously.

In another aspect, the invention includes a pharmaceutical composition comprising a compound of the present invention, and a pharmaceutically acceptable excipient and optionally anti-psychotic agent(s), e.g., at least one. The invention also includes the pharmaceutical composition, where said compound and said agent are to be independently administered rectally, topically, orally, sublingually, or parenterally for a therapeutically effective interval. The invention also includes the pharmaceutical composition, where said compound is administered in an amount of from about 0.001 to about 100 mg/kg of body weight of said mammal per day. The invention also includes the pharmaceutical composition, where said compound is administered in an amount of from about 0.1 to about 50 mg/kg of body weight of said mammal per day. One of ordinary skill in the art will know how to administer the anti-psychotic agent(s).

The invention also concerns the synthesis of and isolation of stereospecific intermediates and final compounds. Specifically, the present invention concerns the stereoselective synthesis of (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine, or salts thereof. Although there are known procedures for making 1-azabicyclo[3.2.1]octan-3-amine, separation of the different stereoisomers as described herein occurs without using a chiral HPLC separation procedure. The procedure within this invention results in an efficient selective synthesis of (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine.

Another aspect of the present invention includes a method for making (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or salt thereof. One process for producing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or a salt thereof, from (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate, comprises: the process of producing (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride from (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate;

the process of producing (5*R*)-1-azabicyclo[3.2.1]octan-3-one or a salt thereof from (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride;

and the process of producing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or a salt thereof from (5*R*)-1-azabicyclo[3.2.1]octan-3-one or a salt thereof.

Another process comprises: the process of producing (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate from (3*R*)-1-[(*S*)-1-phenethyl]-3-(cyanomethyl)pyrrolidine;

the process of producing (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride from (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate;

the process of producing (5*R*)-1-azabicyclo[3.2.1]octan-3-one or a salt thereof from (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride; and the process of producing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or a salt thereof from (5*R*)-1-azabicyclo[3.2.1]octan-3-one or a salt thereof.

Another process comprises: the process of producing (3*S*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid from (*S*)-(-)- $\alpha$ -methyl benzylamine;

the process of isolating (3*S*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid from a racemic mixture using a precipitating solvent without causing the precipitation of other isomers, where the solvent can include a primary alcohol, including but not limited to methanol;

the process of producing (3*S*)-1-[(*S*)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine from (3*S*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid;

the process of producing (3*S*)-1-[(*S*)-1-phenethyl]-3-(chloromethyl)pyrrolidine from (3*S*)-1-[(*S*)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine;

the process of producing (3*R*)-1-[(*S*)-1-phenethyl]-3-(cyanomethyl)pyrrolidine from (3*S*)-1-[(*S*)-1-phenethyl]-3-(chloromethyl)pyrrolidine;

the process of producing (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate from (3*R*)-1-[(*S*)-1-phenethyl]-3-(cyanomethyl)pyrrolidine;

the process of producing (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride from (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate;

the process of producing (5*R*)-1-azabicyclo[3.2.1]octan-3-one or salt thereof from (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride;

and the process of producing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or salt thereof from (5*R*)-1-azabicyclo[3.2.1]octan-3-one or salt thereof.



Another process comprises: the process of producing (3*S*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid from (*S*)-(-)- $\alpha$ -methyl benzylamine;

the process of producing (3*S*)-1-[(*S*)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine from (3*S*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid;

the process of producing (3*S*)-1-[(*S*)-1-phenethyl]-3-(chloromethyl)pyrrolidine from (3*S*)-1-[(*S*)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine;

the process of producing (3*R*)-1-[(*S*)-1-phenethyl]-3-(cyanomethyl)pyrrolidine from (3*S*)-1-[(*S*)-1-phenethyl]-3-(chloromethyl)pyrrolidine;

the process of producing (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate from (3*R*)-1-[(*S*)-1-phenethyl]-3-(cyanomethyl)pyrrolidine;

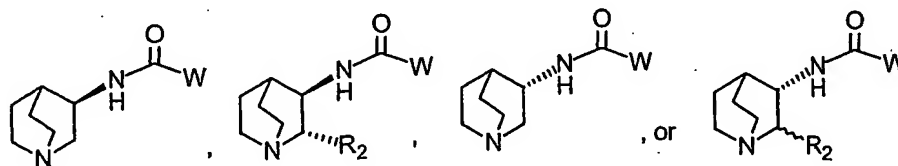
the process of producing (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride from (3*R*)-methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-3-acetate;

the process of producing (5*R*)-1-azabicyclo[3.2.1]octan-3-one or salt thereof from (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride;

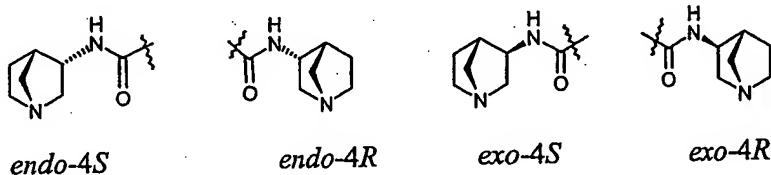
and the process of producing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine or salt thereof from (5*R*)-1-azabicyclo[3.2.1]octan-3-one or salt thereof.

The present invention also includes the compounds of the present invention, pharmaceutical compositions containing the active compounds, and methods to treat the identified diseases.

The compounds of Formula I (Azabicyclo is I) have asymmetric centers on the quinuclidine ring. The compounds of the present invention include quinuclidines with the 3*R* configuration, the 2*S*,3*R* configuration, the 3*S* configuration, the 3*S* configuration and racemic at C-2, and also includes racemic mixtures, the separate stereoisomers, and compositions of varying degrees of stereochemical purity. For example, and not by limitation, compounds of Formula I include compounds with stereospecificity including either of the following:



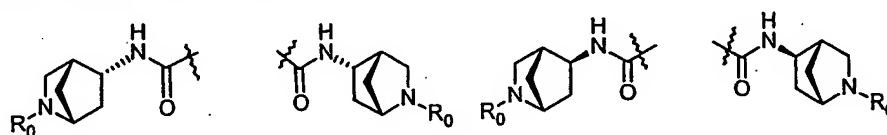
The compounds of Formula I (Azabicyclo II) have asymmetric center(s) on the [2.2.1] azabicyclic ring at C3 and C4. The scope of this invention includes racemic mixtures of varying degrees of stereochemical purities, the separate stereoisomers, and compositions of varying degrees of stereochemical purities of Formula I being *endo*-4*S*, *endo*-4*R*, *exo*-4*S*, *exo*-4*R*:



The *endo* isomer is the isomer where the non-hydrogen substituent at C3 of the [2.2.1] azabicyclic compound is projected toward the larger of the two remaining bridges.

The *exo* isomer is the isomer where the non-hydrogen substituent at C3 of the [2.2.1] azabicyclic compound is projected toward the smaller of the two remaining bridges. Thus, there can be four separate isomers: *exo*-4(*R*), *exo*-4(*S*), *endo*-4(*R*), and *endo*-4(*S*).

The compounds of Formula I (Azabicyclo III) have asymmetric center(s) on the [2.2.1] azabicyclic ring at C1, C4 and C5. The scope of this invention includes racemic mixtures of varying degrees of stereochemical purities, the separate stereoisomers, and compositions of varying degrees of stereochemical purities of Formula I being (1*R*,4*R*,5*S*), (1*R*,4*R*,5*R*), (1*S*,4*S*,5*R*), (1*S*,4*S*,5*S*):



*endo*-1*R*,4*R*,5*R*                      *endo*-1*S*,4*S*,5*S*                      *exo*-1*R*,4*R*,5*S*                      *exo*-1*S*,4*S*,5*R*

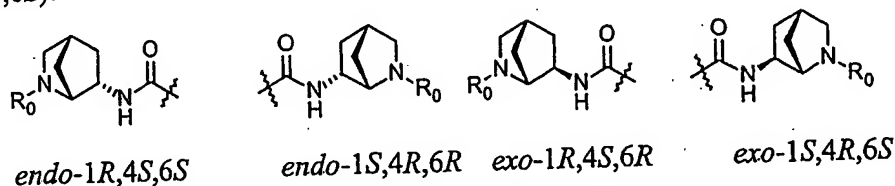
The *endo* isomer is the isomer where the non-hydrogen substituent at C5 of the [2.2.1] azabicyclic compound is projected toward the larger of the two remaining bridges.

The *exo* isomer is the isomer where the non-hydrogen substituent at C5 of the [2.2.1] azabicyclic compound is projected toward the smaller of the two remaining bridges.

Thus, there can be four separate isomers: *exo*-(1*R*,4*R*,5*S*), *exo*-(1*S*,4*S*,5*R*), *endo*-(1*S*,4*S*,5*S*), *endo*-(1*R*,4*R*,5*R*).

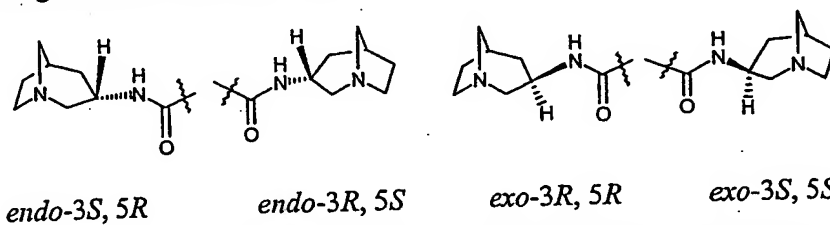
The compounds of Formula I (Azabicyclo IV) have asymmetric center(s) on the [2.2.1] azabicyclic ring at C1, C4 and C6. The scope of this invention includes racemic mixtures of varying degrees of stereochemical purities, the separate stereoisomers, and compositions of varying degrees of stereochemical purities of

Formula I being *exo*-(1*S*,4*R*,6*S*), *exo*-(1*R*,4*S*,6*R*), *endo*-(1*S*,4*R*,6*R*), and *endo*-(1*R*,4*S*,6*S*):

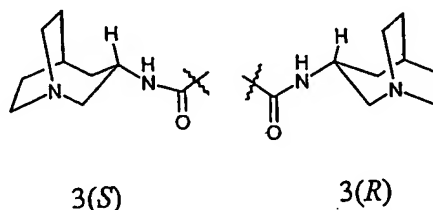


- 5 The *endo* isomer is the isomer where the non-hydrogen substituent at C6 of the [2.2.1] azabicyclic compound is projected toward the larger of the two remaining bridges. The *exo* isomer is the isomer where the non-hydrogen substituent at C6 of the [2.2.1] azabicyclic compound is projected toward the smaller of the two remaining bridges. Thus, there can be four separate isomers: *exo*-(1*S*,4*R*,6*S*), *exo*-(1*R*,4*S*,6*R*), *endo*-(1*S*,4*R*,6*R*), and *endo*-(1*R*,4*S*,6*S*).

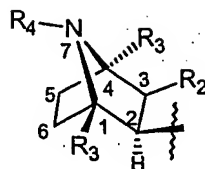
- 10 The compounds of Formula I (Azabicyclo is V) have asymmetric center(s) on the [3.2.1] azabicyclic ring at C3 and C5. The scope of this invention includes racemic mixtures of varying degrees of stereochemical purities, the separate stereoisomers, and compositions of varying degrees of stereochemical purities of Formula I being *endo*-3*S*, 5*R*, *endo*-3*R*, 5*S*, *exo*-3*R*, 5*R*, *exo*-3*S*, 5*S*:



- 20 The compounds of Formula I (Azabicyclo is VI) have asymmetric centers on the [3.2.2] azabicyclic ring with one center being at C3 when R<sub>2</sub> is absent. The scope of this invention includes racemic mixtures of varying degrees of stereochemical purities, the separate stereoisomers, and compositions of varying degrees of stereochemical purities of Formula I being 3(*S*) and 3(*R*):



- 25 The compounds of Formula I where Azabicyclo is VII have asymmetric centers on the 7-azabicyclo[2.2.1]heptane ring which can exhibit a number of stereochemical configurations.



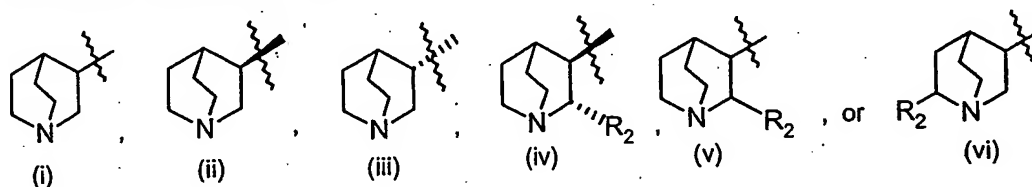
The terms *exo* and *endo* are stereochemical prefixes that describe the relative configuration of a substituent on a bridge (not a bridgehead) of a bicyclic system. If a substituent is oriented toward the larger of the other bridges, it is *endo*. If a substituent is oriented toward the smaller bridge it is *exo*. Depending on the substitution on the carbon atoms, the *endo* and *exo* orientations can give rise to different stereoisomers. For instance, when carbons 1 and 4 are substituted with hydrogen and carbon 2 is bonded to a nitrogen-containing species, the *endo* orientation gives rise to the possibility of a pair of enantiomers: either the *1S*, *2S*, *4R* isomer or its enantiomer, the *1R*, *2R*, *4S* isomer. Likewise, the *exo* orientation gives rise to the possibility of another pair of stereoisomers which are diastereomeric and C-2 epimeric with respect to the *endo* isomers: either the *1R*, *2S*, *4S* isomer or its enantiomer, the *1S*, *2R*, *4R* isomer. The compounds of this invention exist in the *exo* orientation. For example, when  $R_2 = R_3 = H$ , the absolute stereochemistry is *exo*-(*1S*, *2R*, *4R*).

The compounds of the present invention for Azabicyclo is VII have the *exo* orientation at the C-2 carbon and *S* configuration at the C-1 carbon and the *R* configuration at the C-2 and the C-4 carbons of the 7-azabicyclo[2.2.1]heptane ring. Unexpectedly, the inventive compounds exhibit much higher activity relative to compounds lacking the *exo 2R* stereochemistry. For example, the ratio of activities for compounds having the *exo 2R* configuration to other stereochemical configurations may be greater than about 100:1. Although it is desirable that the stereochemical purity be as high as possible, absolute purity is not required. For example, pharmaceutical compositions can include one or more compounds, each having an *exo 2R* configuration, or mixtures of compounds having *exo 2R* and other configurations. In mixtures of compounds, those species possessing stereochemical configurations other than *exo 2R* act as diluents and tend to lower the activity of the pharmaceutical composition. Typically, pharmaceutical compositions including mixtures of compounds possess a larger percentage of species having the *exo 2R* configuration relative to other configurations.

The compounds of the present invention having the specified stereochemistry have different levels of activity and that for a given set of values for the variable substituents one isomer may be preferred over the other isomers. Although it is desirable that the stereochemical purity be as high as possible, absolute purity is not required. This invention involves racemic mixtures and compositions of varying degrees of stereochemical purities for the whole molecule, including the Azabicyclo moiety and the bicyclic fused ring moiety. This invention involves racemic mixtures and compositions of varying degrees of stereochemical purities. When racemic mixtures and compositions are referenced, it is meant racemic mixtures and compositions of varying degrees of stereochemical purities. It is preferred to carry out stereoselective syntheses and/or to subject the reaction product to appropriate purification steps so as to produce substantially enantiomerically pure materials. Suitable stereoselective synthetic procedures for producing enantiomerically pure materials are well known in the art, as are procedures for purifying racemic mixtures into enantiomerically pure fractions.

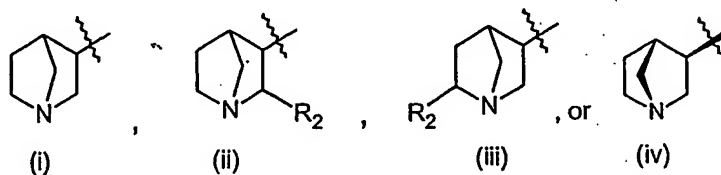
Stereoselective syntheses and/or subjecting the reaction product to appropriate purification steps produce substantially enantiomerically pure materials. Suitable stereoselective synthetic procedures for producing enantiomerically pure materials are well known in the art, as are procedures for purifying racemic mixtures into enantiomerically pure fractions.

Another embodiment of the present invention includes a group of compounds of Formula I that is any one or more or combination of the following:



- wherein (i) the Azabicyclo is a racemic mixture;  
 (ii) the Azabicyclo has the stereochemistry of 3*R* at C3;  
 (iii) the Azabicyclo has the stereochemistry of 3*S* at C3;  
 (iv) the Azabicyclo has the 2*S*,3*R* stereochemistry at C2 and C3, respectively, and  $R_2$  has any definition or specific value discussed herein;  
 (v)  $R_2$  has any definition or specific value discussed herein and is at C-2; or  
 (vi)  $R_2$  has any definition or specific value discussed herein and is at C-6.

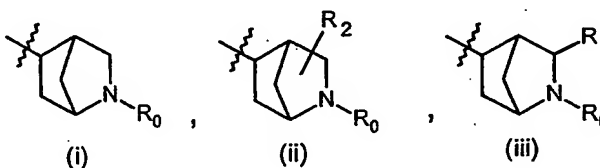
Another embodiment of compounds of Formula I includes any one or more or combination of the following configurations for Azabicyclo:



where (i)  $k_2$  is 0 ( $R_2$  is absent);

- 5 (ii)  $R_2$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;  
 (iii)  $R_2$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or  
 (iv) the 2.2.1 moiety has the *exo*-4(*S*) stereochemistry as discussed herein.

Another embodiment of compounds of Formula I includes any one or more or combination of the following configurations for Azabicyclo:



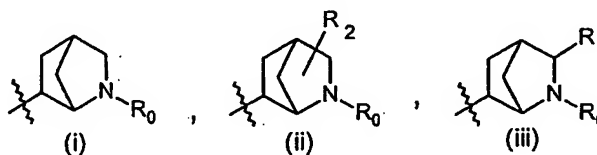
10

where (i)  $R_2$  is H;

- (ii)  $R_2$  is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or  
 (iii)  $R_2$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl.

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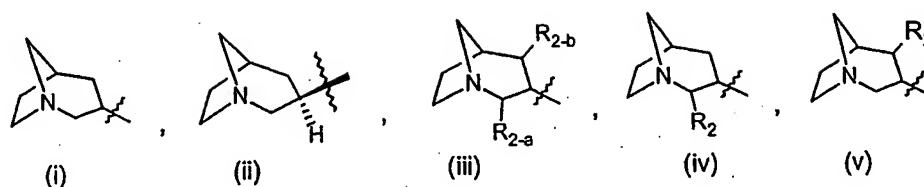
Another embodiment of compounds of Formula I includes any one or more or combination of the following configurations for Azabicyclo:



where (i)  $R_2$  is H;

- (ii)  $R_2$  is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or  
 20 aryl; or  
 (iii)  $R_2$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl.

Another embodiment of compounds of Formula I includes any one or more or combination of the following configurations for Azabicyclo:



where (i)  $k_5$  is 0 ( $R_2$  is absent);

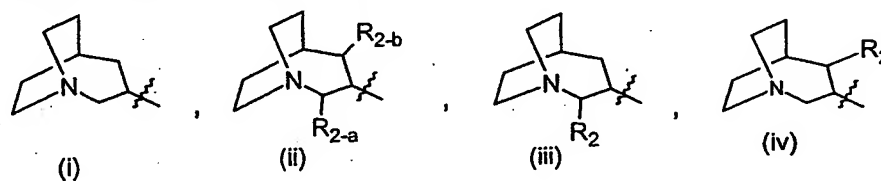
(ii)  $R_2$  is absent and where the Azabicyclo has the stereochemistry of 3*R*, 5*R*;

(iii)  $k_5$  is 2, where  $R_{2-a}$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl, and where  $R_{2-b}$  is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

(iv)  $k_5$  is 1, where  $R_2$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

(v)  $k_5$  is 1, where  $R_2$  is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl.

Another embodiment of compounds of Formula I includes any one or more or combination of the following configurations for Azabicyclo:



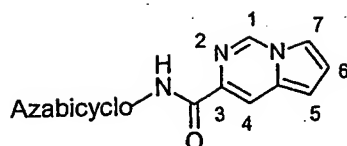
where (i)  $k_6$  is 0 ( $R_2$  is absent);

(ii)  $k_6$  is 2, where each  $R_{2-a}$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl and where each  $R_{2-b}$  is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

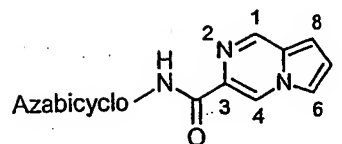
(iii)  $k_6$  is 1, where  $R_2$  is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

(iv)  $k_6$  is 1, where  $R_2$  is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl.

Surprisingly, we have found that it is important for the amide bond between the azabicyclic moiety and the W moiety to be attached at C-3 of the pyrrolo[1,2-*c*]pyrimidinyl moiety and the pyrrolo[1,2-*a*]pyrazinyl moiety. When W is a bicyclic-fused moiety, Formula I would be (where each  $R_5$  is H):

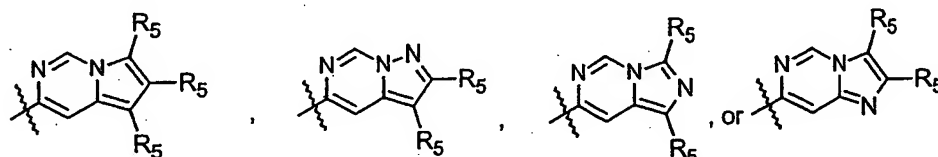


W is pyrrolo[1,2-c]pyrimidinyl



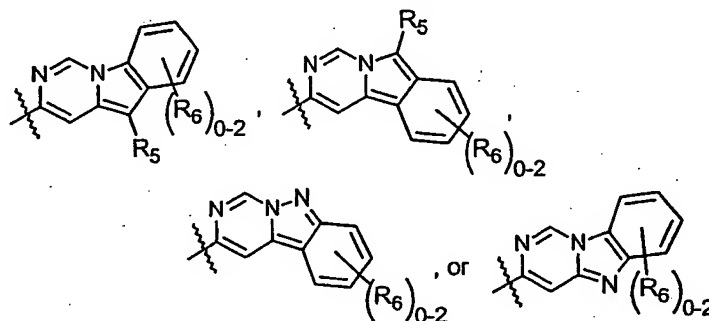
W is pyrrolo[1,2-a]pyrazinyl

Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



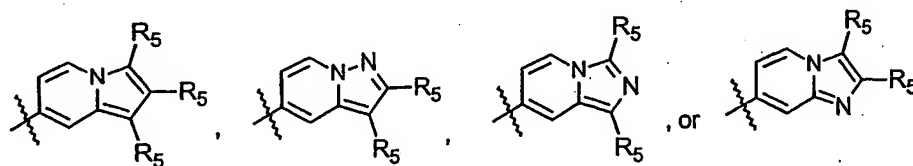
5 where  $R_5$  has any value described herein.

Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



where  $R_5$  and  $R_6$  have any value described herein.

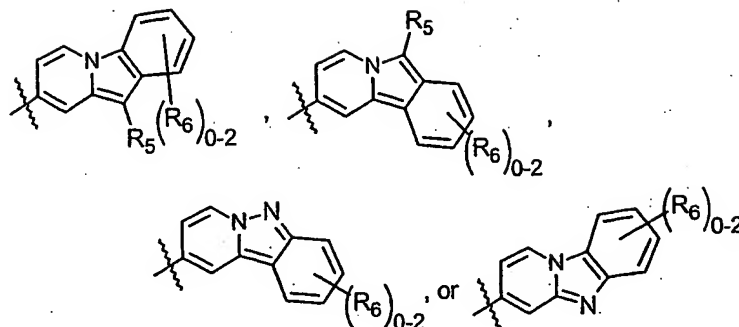
10 Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



where  $R_5$  has any value described herein.

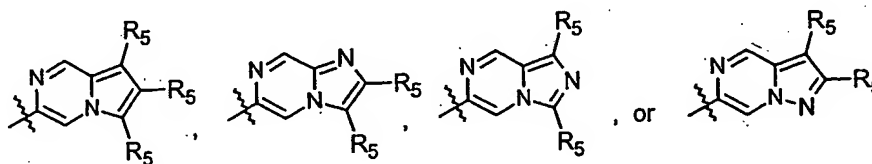
15 Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:





where  $R_5$  and  $R_6$  have any value described herein.

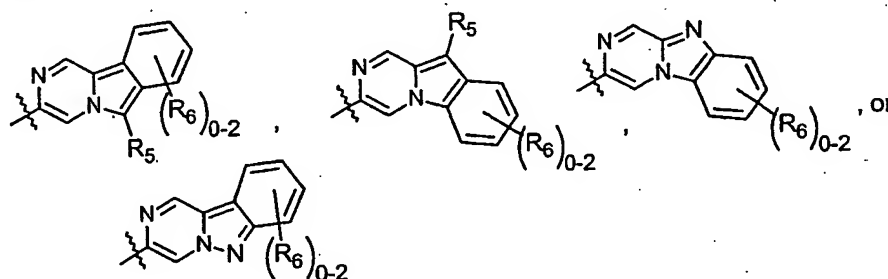
Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



5

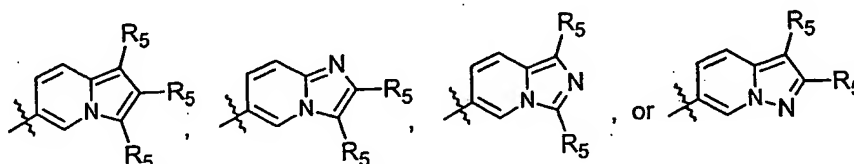
where  $R_5$  has any value described herein.

Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



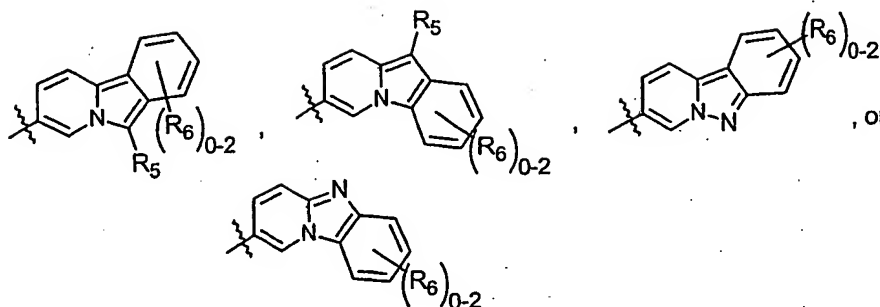
10 where  $R_5$  and  $R_6$  have any value described herein.

Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



where  $R_5$  has any value described herein.

15 Another group of compounds of Formula I includes compounds where W includes any one of or combination of the following:



where  $R_5$  and  $R_6$  have any value described herein.

Another group of compounds of Formula I includes compounds, where Azabicyclo is any one or more of the following: I, II, III, IV, V, VI, or VII. Another group of compounds of Formula I includes compounds, where  $k$  is 1 or 2.

Another group of compounds of Formula I includes compounds, where  $R_0$  is H. Other compounds within the scope of the present invention are where  $R_0$  is methyl. Other compounds within the scope of the present invention are where  $R_0$  is lower alkyl, lower substituted alkyl, or lower halogenated alkyl.

Another group of compounds of Formula I includes compounds where  $R_1$  is H. Another group of compounds of Formula I includes compounds where  $R_1$  is any one or more of the following: H, alkyl, or haloalkyl. Another group of compounds of Formula I includes compounds where  $R_2$  is H. Another group of compounds of Formula I includes compounds where each  $R_2$  is any one or more of the following: H, F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl. Another group of compounds of Formula I includes compounds where each  $R_2$  is any one of H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl. Another group of compounds of Formula I includes compounds where each  $R_2$  is methyl.

Another group of compounds of Formula I includes compounds where each  $R_3$  is H. Another group of compounds of Formula I includes compounds where each  $R_3$  is independently any one or more of the following: H, alkyl, or substituted alkyl. Another group of compounds of Formula I includes compounds where  $R_4$  is H. Another group of compounds of Formula I includes compounds where  $R_4$  is any one or more of the following: H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, -OH, -CN, -NH<sub>2</sub>, -NH(alkyl), or -N(alkyl)<sub>2</sub>. Another group of compounds of Formula I includes compounds where  $R_4$  is any one or more of the following: H, lower alkyl optionally substituted with up to 3

substituents independently selected from F, Cl, Br, I, -OH, -CN, -NH<sub>2</sub>, -NH(lower alkyl), or -N(lower alkyl)<sub>2</sub>.

Another group of compounds of Formula I includes compounds, where W is (a) or (b). Another group of compounds of Formula I includes compounds, where W<sup>1</sup> is N or CH. Another group of compounds of Formula I includes compounds, where each W<sup>2</sup> is N or C(R<sub>5</sub>), provided that no more than one W<sup>2</sup> is N.

Another group of compounds of Formula I includes compounds where each R<sub>5</sub> is H. Another group of compounds of Formula I includes compounds where each R<sub>5</sub> is independently any one or more of the following: H, alkyl, substituted alkyl, halogenated alkyl, alkenyl, substituted alkenyl, halogenated alkenyl, alkynyl, substituted alkynyl, halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, aryl, R<sub>7</sub>, or R<sub>9</sub>.

Another group of compounds of Formula I includes compounds where each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>, wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

Another group of compounds of Formula I includes compounds where two R<sub>5</sub> on adjacent carbons may combine for W to be a fused-tricyclic-heteroaromatic-ring system having substitution as allowed by formula I and discussed herein.

Another group of compounds of Formula I includes compounds where R<sub>6</sub> is any one or more of the following: alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -NR<sub>8</sub>R<sub>8</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)NR<sub>8</sub>R<sub>8</sub>, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, phenyl, phenyl having 0-4 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>, naphthyl, or naphthyl having 0-4 substituents independently selected from F, Cl, Br, I, or R<sub>15</sub>.

Another group of compounds of Formula I includes compounds where each  $R_6$  is F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl,  $-OR_8$ ,  $-SR_8$ ,  $-S(O)_2R_8$ ,  $-S(O)R_8$ ,  $-OS(O)_2R_8$ ,  $-N(R_8)_2$ ,  $-C(O)R_8$ ,  $-C(S)R_8$ ,  $-C(O)OR_8$ ,  $-CN$ ,  $-C(O)N(R_8)_2$ ,  $-NR_8C(O)R_8$ ,  $-S(O)_2N(R_8)_2$ ,  $-NR_8S(O)_2R_8$ ,  $-NO_2$ ,  $-N(R_8)C(O)N(R_8)_2$ , lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and  $R_{15}$ , wherein each  $R_8$  is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or  $R_{15}$ .

Another group of compounds of Formula I includes compounds where each  $R_9$  is independently any one or more of the following: H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or  $R_{15}$ .

Another group of compounds of Formula I includes compounds where each  $R_{10}$  is independently any one or more of the following: H, alkyl, cycloalkyl, heterocycloalkyl, alkyl substituted with 1 substituent selected from  $R_{13}$ , cycloalkyl substituted with 1 substituent selected from  $R_{13}$ , heterocycloalkyl substituted with 1 substituent selected from  $R_{13}$ , halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, phenyl, or substituted phenyl.

Another group of compounds of Formula I includes compounds where each  $R_{11}$  is independently any one or more of the following: H, alkyl, cycloalkyl, heterocyclo-alkyl, halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl.

Another group of compounds of Formula I includes compounds where  $R_{12}$  is any one or more of the following:  $-OR_{11}$ ,  $-SR_{11}$ , alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl,  $-NR_{11}R_{11}$ ,  $-C(O)R_{11}$ ,  $-NO_2$ ,  $-C(O)NR_{11}R_{11}$ ,  $-CN$ ,  $-NR_{11}C(O)R_{11}$ ,  $-S(O)_2NR_{11}R_{11}$ , or  $-NR_{11}S(O)_2R_{11}$ .

Another group of compounds of Formula I includes compounds where  $R_{13}$  is any one or more of the following:  $-OR_{11}$ ,  $-SR_{11}$ ,  $-NR_{11}R_{11}$ ,  $-C(O)R_{11}$ ,  $-SOR_{11}$ ,  $-SO_2R_{11}$ ,  $-C(O)NR_{11}R_{11}$ ,  $-CN$ ,  $-CF_3$ ,  $-NR_{11}C(O)R_{11}$ ,  $-S(O)_2NR_{11}R_{11}$ ,  $-NR_{11}S(O)_2R_{11}$ , or  $-NO_2$ .

5 Another group of compounds of Formula I includes compounds where  $R_{14}$  is independently any one or more of the following: H, alkyl, halogenated alkyl, limited substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, or substituted heterocycloalkyl.

10 Another group of compounds of Formula I includes compounds where  $R_{15}$  is any one or more of the following: alkyl, substituted alkyl, halogenated alkyl,  $-OR_{11}$ ,  $-CN$ ,  $-NO_2$ ,  $-NR_{10}R_{10}$ .

Another group of compounds of Formula I includes compounds where  $R_{16}$  is any one or more of the following: H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, phenyl, or phenyl having  
15 0-4 substituents independently selected from F, Cl, Br, I, and  $R_{15}$ .

One of ordinary skill in the art will recognize that where alkyl, substituted alkyl, halogenated alkyl, alkenyl, substituted alkenyl, halogenated alkenyl, alkynyl, substituted alkynyl, or halogenated alkynyl is allowed, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower  
20 halogenated alkenyl, lower alkynyl, lower substituted alkynyl, or lower halogenated alkynyl, respectively, is also allowed.

Another group of compounds of Formula I includes any one or more of the following compounds as the free base or pharmaceutically acceptable salt thereof and as the pure enantiomer or racemic mixture thereof (naming specific enantiomers is for  
25 exemplification and does not limit the scope of the present invention):

*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

*N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

30 *N*-[(3*R*,4*S*)-1-azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

*N*-[(1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]hept-2-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide;

*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-*a*]pyridine-7-carboxamide;

*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyridine-7-carboxamide;

- N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyridine-6-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-*a*]pyridine-6-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide;  
*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide;  
5 *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
*N*-[(1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]hept-2-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
*N*-[(3*R*,4*S*)-1-azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
*N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]pyrazino[1,2-*a*]indole-3-carboxamide;  
10 *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyrazine-6-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-ethynylpyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-prop-1-ynylpyrrolo[1,2-*a*]pyrazine-3-  
carboxamide;  
15 *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo [1,2-  
*a*]pyrazine-3-carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-cyanopyrrolo[1,2-*a*]pyrazine-3-carboxamide;  
7-Chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-  
3-carboxamide;  
20 6-Chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-  
3-carboxamide;  
*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-  
carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-chloropyrrolo[1,2-*c*]pyrimidine-3-  
25 carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloropyrrolo[1,2-*c*]pyrimidine-3-  
carboxamide;  
*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*c*]pyrimidine-3-  
carboxamide;  
30 *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*c*]pyrimidine-7-carboxamide;  
*N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide; or  
*N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide.

Another group of compounds of Formula I includes any one or more of the following compounds as the free base or pharmaceutically acceptable salt thereof and as the pure enantiomer or racemic mixture thereof (naming specific enantiomers is for exemplification and does not limit the scope of the present invention):

- 5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-methylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-chloroindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-bromoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-cyanoindolizine-6-carboxamide;
- 10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-ethynylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoindolizine-6-carboxamide;
- 15 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-methylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-chloroindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-bromoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-cyanoindolizine-6-carboxamide;
- 20 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-ethynylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]indolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-methylindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-chloroindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-bromoindolizine-7-carboxamide;
- 25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-cyanoindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-ethynylindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoindolizine-7-carboxamide;
- 30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-methylindolizine-7-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-chloroindolizine-7-carboxamide;

- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-bromoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
15 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;  
20 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]pyrido[1,2-a]indole-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-9H-carbazole-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;



- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;  
10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-  
15 carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
20 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-  
25 carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;

- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;  
10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]pyrazino[1,2-a]indole-3-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-9H-beta-carboline-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]indolizine-6-carboxamide;  
15 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-methylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-chloroindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-bromoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-cyanoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-ethynylindolizine-6-carboxamide;  
20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylindolizine-6-carboxamide;  
25 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-methylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-chloroindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-bromoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-cyanoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-ethynylindolizine-6-carboxamide;  
30 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]indolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-methylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-chloroindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-bromoindolizine-7-carboxamide;

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-ethynylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroindolizine-7-carboxamide;  
5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-methylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-chloroindolizine-7-carboxamide;  
10 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-bromoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
15 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
25 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
30 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;
- 5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrido[1,2-a]indole-7-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-9H-carbazole-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 10 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-
- 15 carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo [1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-
- 25 carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 30 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- 5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;
- 10 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-
- 15 carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-
- 25 carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 30 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;
- 10 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrazino[1,2-a]indole-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-9H-beta-carboline-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]indolizine-6-carboxamide;
- 15 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-methylindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-chloroindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-bromoindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-cyanoindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-ethynylindolizine-6-carboxamide;
- 20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylindolizine-6-carboxamide;
- 25 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-methylindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-chloroindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-bromoindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-cyanoindolizine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-ethynylindolizine-6-carboxamide;
- 30 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]indolizine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-methylindolizine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-chloroindolizine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-bromoindolizine-7-carboxamide;

- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-cyanoindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-ethynylindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroindolizine-7-carboxamide;  
 5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-methylindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-chloroindolizine-7-carboxamide;  
 10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-bromoindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-cyanoindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-ethynylindolizine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
 15 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
 20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
 25 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
 30 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;

- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;
- 5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]pyrido[1,2-a]indole-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-9H-carbazole-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-
- 15 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-
- 25 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 30 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;



- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- 5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;
- 10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-
- 15 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-
- 25 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 30 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;

5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[ (3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;

10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]pyrazino[1,2-a]indole-3-carboxamide;

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-9H-beta-carboline-3-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]indolizine-6-carboxamide;

15 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-methylindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-chloroindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-bromoindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-cyanoindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-ethynylindolizine-6-carboxamide;

20 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylindolizine-6-carboxamide;

25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-methylindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-chloroindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-bromoindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-cyanoindolizine-6-carboxamide;

N-[**(3R)**-1-azabicyclo[3.2.1]non-3-yl]-3-ethynylindolizine-6-carboxamide;

30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]indolizine-7-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-methylindolizine-7-carboxamide;

N-[3(R)-1-azabicyclo[3.2.1]non-3-yl]-1-chloroindolizine-7-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-bromoindolizine-7-carboxamide;

- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroindolizine-7-carboxamide;  
5 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-methylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-chloroindolizine-7-carboxamide;  
10 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-bromoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
15 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-  
20 carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]pyrido[1,2-a]indole-7-carboxamide;

- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-9H-carbazole-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 5 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-  
 carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-  
 10 carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-  
 a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 15 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-  
 carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 20 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-  
 carboxamide;  
 25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-  
 carboxamide;  
 30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-  
 carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-  
 carboxamide;

- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-
- 10 carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 15 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-
- 20 carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]pyrazino[1,2-a]indole-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-9H-beta-carboline-3-carboxamide;
- 30 N-[2-azabicyclo[2.2.1]hept-5-yl]indolizine-6-carboxamide;
- N-[2-azabicyclo[2.2.1]hept-5-yl]-1-methylindolizine-6-carboxamide;
- N-[2-azabicyclo[2.2.1]hept-5-yl]-1-chloroindolizine-6-carboxamide;
- N-[2-azabicyclo[2.2.1]hept-5-yl]-1-bromoindolizine-6-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-5-yl]-1-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-1-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroindolizine-6-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-chloroindolizine-6-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-bromoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]indolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-1-methylindolizine-7-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-1-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-1-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-1-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylindolizine-7-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-methylindolizine-7-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-5-yl]pyrido[1,2-a]indole-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-9H-carbazole-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-5-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-  
20 carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-5-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-5-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-a]pyrazine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-5-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-5-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-5-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-5-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]pyrazino[1,2-a]indole-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-9H-beta-carboline-3-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-6-yl]indolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-chloroindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-bromoindolizine-6-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-6-yl]-1-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoindolizine-6-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-chloroindolizine-6-carboxamide;



- N-[2-azabicyclo[2.2.1]hept-6-yl]-3-bromoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]indolizine-7-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-6-yl]-1-methylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-ethynylindolizine-7-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylindolizine-7-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-6-yl]-3-methylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-ethynylindolizine-7-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-6-yl]pyrido[1,2-a]indole-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-9H-carbazole-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-6-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-a]pyrazine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-6-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-6-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]pyrazino[1,2-a]indole-3-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-6-yl]-9H-beta-carboline-3-carboxamide;  
  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]indolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-methylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-chloroindolizine-6-carboxamide;  
15 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-bromoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-cyanoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-ethynylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroindolizine-6-carboxamide;  
20 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-methylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-chloroindolizine-6-carboxamide;  
25 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-bromoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-cyanoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-ethynylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]indolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-methylindolizine-7-carboxamide;  
30 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-chloroindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-bromoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-ethynylindolizine-7-carboxamide;

- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoindolizine-7-carboxamide;  
5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-methylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-chloroindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-bromoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-cyanoindolizine-7-carboxamide;  
10 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylimidazo[1,2-a]pyridine-6-  
15 carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroimidazo[1,2-a]pyridine-6-  
carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoimidazo[1,2-a]pyridine-6-  
carboxamide;  
20 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoimidazo[1,2-a]pyridine-6-  
carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylimidazo[1,2-a]pyridine-6-  
carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
25 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylimidazo[1,2-a]pyridine-7-  
carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroimidazo[1,2-a]pyridine-7-  
carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoimidazo[1,2-a]pyridine-7-  
30 carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoimidazo[1,2-a]pyridine-7-  
carboxamide;

- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]pyrido[1,2-a]indole-7-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-9H-carbazole-3-carboxamide;
- 5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 10 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-
- 15 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
- 20 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-
- 25 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 30 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;

- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-a]pyrazine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-a]pyrazine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-pyrrolo[1,2-c]pyrimidine-3-
- 10 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 15 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-
- 20 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 25 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-
- 30 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-c]pyrimidine-7-
- 10 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]pyrazino[1,2-a]indole-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-9H-beta-carboline-3-carboxamide;

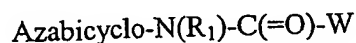
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Further aspects and embodiments of the invention may become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the examples and the appended claims. While the invention is susceptible of embodiments in various forms, described hereafter are specific

20 embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

## DETAILED DESCRIPTION OF THE INVENTION

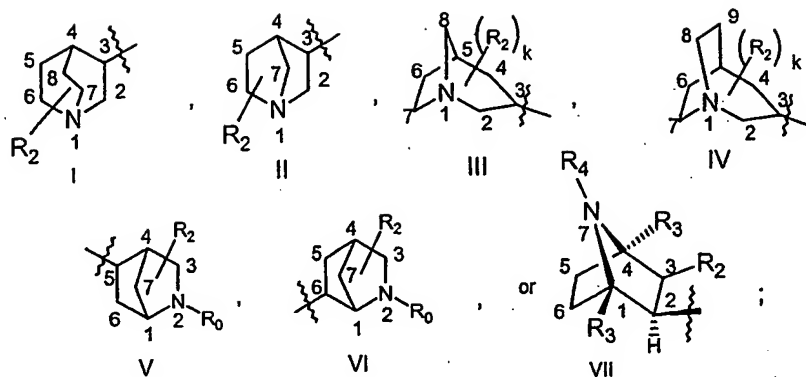
25 Surprisingly, we have found that compounds of Formula I:



Formula I

wherein R<sub>1</sub> is H, alkyl, or haloalkyl;

Azabicyclo is



$R_0$  is H, lower alkyl, lower substituted alkyl, or lower halogenated alkyl;

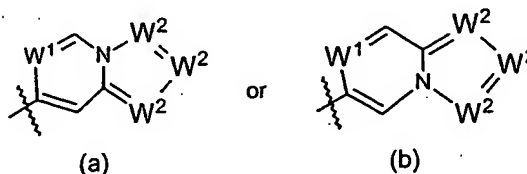
$R_2$  is H, F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

$k$  is 1 or 2, provided that when  $k$  is 2, one  $R_2$  is other than H;

Each  $R_3$  is independently H, alkyl, or substituted alkyl;

$R_4$  is H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, -OH, -CN, -NH<sub>2</sub>, -NH(alkyl), or -N(alkyl)<sub>2</sub>;

W is



wherein  $W^1$  is N or CH;

Each  $W^2$  is N or C( $R_5$ ), provided that no more than one  $W^2$  is N;

Each  $R_5$  is independently H, alkyl, substituted alkyl, halogenated alkyl, alkenyl, substituted alkenyl, halogenated alkenyl, alkynyl, substituted alkynyl,

halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N( $R_{10}$ )<sub>2</sub>, -N( $R_{10}$ )<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, aryl,  $R_7$ ,  $R_9$ , or two  $R_5$  on adjacent carbon atoms may combine for W to be a 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with 1-2 substituents independently selected from F, Cl, Br, I, and  $R_6$ ;

$R_6$  is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -NR<sub>8</sub>R<sub>8</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>,



-NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)NR<sub>8</sub>R<sub>8</sub>, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, phenyl, phenyl having 0-4 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>, naphthyl, or naphthyl having 0-4 substituents independently selected from F, Cl, Br, I, or R<sub>15</sub>;

Alkyl is both straight- and branched-chain moieties having from 1-6 carbon atoms;

Lower alkyl is both straight- and branched-chain moieties having from 1-4 carbon atoms;

Halogenated alkyl is an alkyl moiety having from 1-6 carbon atoms and having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Lower halogenated alkyl is an alkyl moiety having from 1-4 carbon atoms and having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Substituted alkyl is an alkyl moiety from 1-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from R<sub>7</sub>, R<sub>9</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>10</sub>, -C(O)R<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>10</sub>, -CN, -NR<sub>10</sub>C(O)R<sub>10</sub>, -S(O)<sub>2</sub>NR<sub>10</sub>R<sub>10</sub>, -NR<sub>10</sub>S(O)<sub>2</sub>R<sub>10</sub>, -NO<sub>2</sub>, phenyl, or phenyl having 1 substituent selected from R<sub>15</sub> and further having 0-3 substituents independently selected from F, Cl, Br, or I;

Lower substituted alkyl is lower alkyl having 0-3 substituents independently selected from F, Cl, Br, or I, and further having 1 substituent selected from -OR<sub>10</sub>, -SR<sub>10</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -C(O)R<sub>10</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -CN, -NR<sub>10</sub>C(O)R<sub>10</sub>, -S(O)<sub>2</sub>N(R<sub>10</sub>)<sub>2</sub>, -NR<sub>10</sub>S(O)<sub>2</sub>R<sub>10</sub>, -NO<sub>2</sub>, phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, cycloalkyl, heterocycloalkyl, or phenyl,

wherein any lower alkyl, cycloalkyl, heterocycloalkyl, or phenyl is optionally substituted with up to two halogens independently selected from F or Cl

wherein any lower alkyl, cycloalkyl, or heterocycloalkyl is further optionally substituted with 1 substituent selected from -OR<sub>11</sub>, -SR<sub>11</sub>, -N(R<sub>11</sub>)<sub>2</sub>, -C(O)R<sub>11</sub>, -C(O)N(R<sub>11</sub>)<sub>2</sub>, -CN, -CF<sub>3</sub>, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>N(R<sub>11</sub>)<sub>2</sub>, -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>, or -NO<sub>2</sub>,

and wherein each  $R_{11}$  is independently H, lower alkyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

Alkenyl is straight- and branched-chain moieties having from 2-6 carbon atoms and having at least one carbon-carbon double bond;

Lower alkenyl is straight- and branched-chain moieties having from 2-4 carbon atoms and having at least one carbon-carbon double bond;

Halogenated alkenyl is an unsaturated alkenyl moiety having from 2-6 carbon atoms and having 1 to  $(2n-1)$  substituent(s) independently selected from F, Cl, Br, or I where  $n$  is the maximum number of carbon atoms in the moiety;

Lower halogenated alkenyl is an unsaturated alkenyl moiety having from 2-4 carbon atoms and having 1 to  $(2n-1)$  substituent(s) independently selected from F, Cl, Br, or I where  $n$  is the maximum number of carbon atoms in the moiety;

Substituted alkenyl is alkenyl having 0-2 substituents independently selected from F, or Cl, and further having 1 substituent selected from  $R_7$ ,  $R_9$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{10}$ ,  $-C(O)R_{10}$ ,  $-C(O)NR_{10}R_{10}$ ,  $-CN$ ,  $-NR_{10}C(O)R_{10}$ ,  $-S(O)_2NR_{10}R_{10}$ ,  $-NR_{10}S(O)_2R_{10}$ ,  $-NO_2$ , phenyl, or phenyl having 1 substituent selected from  $R_{15}$  and further having 0-3 substituents independently selected from F, Cl, Br, or I;

Lower substituted alkenyl is lower alkenyl having 0-2 substituents independently selected from F, or Cl, and further having 1 substituent selected from  $-OR_{10}$ ,  $-SR_{10}$ ,  $-N(R_{10})_2$ ,  $-C(O)R_{10}$ ,  $-C(O)N(R_{10})_2$ ,  $-CN$ ,  $-NR_{10}C(O)R_{10}$ ,  $-S(O)_2N(R_{10})_2$ ,  $-NR_{10}S(O)_2R_{10}$ ,  $-NO_2$ , phenyl,  $R_7$ , or  $R_9$ ,

wherein each  $R_{10}$  is independently H, lower alkyl, cycloalkyl, heterocycloalkyl, or phenyl,

wherein any lower alkyl, cycloalkyl, heterocycloalkyl, or phenyl is optionally substituted with up to two halogens independently selected from F or Cl

wherein any lower alkyl, cycloalkyl, or heterocycloalkyl is further optionally substituted with 1 substituent selected from  $-OR_{11}$ ,  $-SR_{11}$ ,  $-N(R_{11})_2$ ,  $-C(O)R_{11}$ ,  $-C(O)N(R_{11})_2$ ,  $-CN$ ,  $-CF_3$ ,  $-NR_{11}C(O)R_{11}$ ,  $-S(O)_2N(R_{11})_2$ ,  $-NR_{11}S(O)_2R_{11}$ , or  $-NO_2$ ,

and wherein each  $R_{11}$  is independently H, lower alkyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

Alkynyl is straight- and branched-chained moieties having from 2-6 carbon atoms and having at least one carbon-carbon triple bond;

Lower alkynyl is straight- and branched-chained moieties having from 2-4 carbon atoms and having at least one carbon-carbon triple bond;

5 Halogenated alkynyl is an unsaturated alkynyl moiety having from 3-6 carbon atoms and having 1 to (2n-3) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Lower halogenated alkynyl is an unsaturated alkynyl moiety having from 3-4 carbon atoms and having 1 to (2n-3) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

10 Substituted alkynyl is an unsaturated alkynyl moiety having from 3-6 carbon atoms and having 0-3 substituents independently selected from F, or Cl, and further having 1 substituent selected from R<sub>7</sub>, R<sub>9</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>10</sub>, -C(O)R<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>10</sub>, -NR<sub>10</sub>C(O)R<sub>10</sub>, -S(O)<sub>2</sub>NR<sub>10</sub>R<sub>10</sub>, -NR<sub>10</sub>S(O)<sub>2</sub>R<sub>10</sub>, -CN, phenyl, or  
15 phenyl having 1 substituent selected from R<sub>15</sub>, and further having 0-3 substituents independently selected from F, Cl, Br, or I;

Lower substituted alkynyl is lower alkynyl having 0-2 substituents independently selected from F, or Cl, and further having 1 substituent selected from -OR<sub>10</sub>, -SR<sub>10</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -C(O)R<sub>10</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -CN, -NR<sub>10</sub>C(O)R<sub>10</sub>, -S(O)<sub>2</sub>N(R<sub>10</sub>)<sub>2</sub>,  
20 -NR<sub>10</sub>S(O)<sub>2</sub>R<sub>10</sub>, -NO<sub>2</sub>, phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, cycloalkyl, heterocycloalkyl, or phenyl,

wherein any lower alkyl, cycloalkyl, heterocycloalkyl, or phenyl is optionally substituted with up to two halogens independently selected from F or Cl

25 wherein any lower alkyl, cycloalkyl, or heterocycloalkyl is further optionally substituted with 1 substituent selected from -OR<sub>11</sub>, -SR<sub>11</sub>, -N(R<sub>11</sub>)<sub>2</sub>, -C(O)R<sub>11</sub>, -C(O)N(R<sub>11</sub>)<sub>2</sub>, -CN, -CF<sub>3</sub>, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>N(R<sub>11</sub>)<sub>2</sub>, -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>, or -NO<sub>2</sub>,

and wherein each R<sub>11</sub> is independently H, lower alkyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, halogenated cycloalkyl, or halogenated  
30 heterocycloalkyl;

Cycloalkyl is a cyclic alkyl moiety having from 3-6 carbon atoms;

Halogenated cycloalkyl is a cyclic moiety having from 3-6 carbon atoms and having 1-4 substituents independently selected from F, or Cl;

Substituted cycloalkyl is a cyclic moiety having from 3-6 carbon atoms and having 0-3 substituents independently selected from F, or Cl, and further having 1 substituent selected from -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>10</sub>, -C(O)R<sub>10</sub>, -CN, -C(O)NR<sub>10</sub>R<sub>10</sub>, -NR<sub>10</sub>C(O)R<sub>10</sub>, -S(O)<sub>2</sub>NR<sub>10</sub>R<sub>10</sub>, -NR<sub>10</sub>S(O)<sub>2</sub>R<sub>10</sub>, -NO<sub>2</sub>, phenyl, or phenyl having 1 substituent selected from R<sub>15</sub>, and further having 0-3 substituents independently selected from F, Cl, Br, or I;

Heterocycloalkyl is a cyclic moiety having 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R<sub>16</sub>)-, or -O-;

Halogenated heterocycloalkyl is a cyclic moiety having from 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R<sub>16</sub>)-, or -O-, and having 1-4 substituents independently selected from F, or Cl;

Substituted heterocycloalkyl is a cyclic moiety having from 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R<sub>16</sub>)-, or -O- and having 0-3 substituents independently selected from F, or Cl, and further having 1 substituent selected from R<sub>7</sub>, R<sub>9</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>10</sub>, -C(O)R<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>10</sub>, -CN, -NR<sub>10</sub>C(O)R<sub>10</sub>, -NO<sub>2</sub>, -S(O)<sub>2</sub>NR<sub>10</sub>R<sub>10</sub>, -NR<sub>10</sub>S(O)<sub>2</sub>R<sub>10</sub>, phenyl, or phenyl having 1 substituent selected from R<sub>15</sub> and further having 0-3 substituents independently selected from F, Cl, Br, or I;

Lactam heterocycloalkyl is a cyclic moiety having from 4-7 atoms with one atom being only nitrogen with the bond to the lactam heterocycloalkyl thru said atom being only nitrogen and having a =O on a carbon adjacent to said nitrogen, and having up to 1 additional ring atom being oxygen, sulfur, or nitrogen and further having 0-2 substituents selected from F, Cl, Br, I, or R<sub>15</sub> where valency allows;

Aryl is phenyl, substituted phenyl, naphthyl, or substituted naphthyl;

Substituted phenyl is a phenyl either having 1-4 substituents independently selected from F, Cl, Br, or I, or having 1 substituent selected from R<sub>12</sub> and 0-3 substituents independently selected from F, Cl, Br, or I;

Substituted naphthyl is a naphthalene moiety either having 1-4 substituents independently selected from F, Cl, Br, or I, or having 1 substituent selected from R<sub>12</sub> and 0-3 substituents independently selected from F, Cl, Br, or I, where the substitution can be independently on either only one ring or both rings of said naphthalene moiety;

R<sub>7</sub> is 5-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms independently selected from the group consisting of -O-, =N-,

-N(R<sub>14</sub>)-, and -S-, and having 0-1 substituent selected from R<sub>15</sub>, and further having 0-3 substituents independently selected from F, Cl, Br, or I, wherein the R<sub>7</sub> moiety attaches to other substituents as defined in formula I at any position as valency allows;

Each R<sub>8</sub> is independently H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>;

R<sub>9</sub> is 6-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms selected from =N- and having 0-1 substituent selected from R<sub>15</sub> and 0-3 substituent(s) independently selected from F, Cl, Br, or I, wherein the R<sub>9</sub> moiety attaches to other substituents as defined in formula I at any position as valency allows;

Each R<sub>10</sub> is independently H, alkyl, cycloalkyl, heterocycloalkyl, alkyl substituted with 1 substituent selected from R<sub>13</sub>, cycloalkyl substituted with 1 substituent selected from R<sub>13</sub>, heterocycloalkyl substituted with 1 substituent selected from R<sub>13</sub>, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, phenyl, or substituted phenyl;

Each R<sub>11</sub> is independently H, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

R<sub>12</sub> is -OR<sub>11</sub>, -SR<sub>11</sub>, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, -NR<sub>11</sub>R<sub>11</sub>, -C(O)R<sub>11</sub>, -NO<sub>2</sub>, -C(O)NR<sub>11</sub>R<sub>11</sub>, -CN, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>NR<sub>11</sub>R<sub>11</sub>, or -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>;

R<sub>13</sub> is -OR<sub>11</sub>, -SR<sub>11</sub>, -NR<sub>11</sub>R<sub>11</sub>, -C(O)R<sub>11</sub>, -SOR<sub>11</sub>, -SO<sub>2</sub>R<sub>11</sub>, -C(O)NR<sub>11</sub>R<sub>11</sub>, -CN, -CF<sub>3</sub>, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>NR<sub>11</sub>R<sub>11</sub>, -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>, or -NO<sub>2</sub>;

R<sub>14</sub> is independently H, alkyl, halogenated alkyl, limited substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, or substituted heterocycloalkyl;

R<sub>15</sub> is alkyl, substituted alkyl, halogenated alkyl, -OR<sub>11</sub>, -CN, -NO<sub>2</sub>, -NR<sub>10</sub>R<sub>10</sub>;

R<sub>16</sub> is H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, phenyl, or phenyl having 0-4 substituents independently selected from F, Cl, Br, I, and R<sub>15</sub>;

or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof.

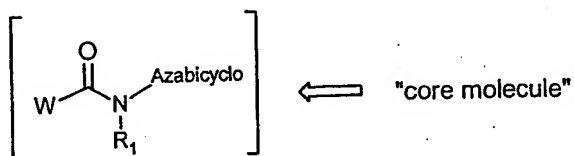
The compounds of the present invention are useful for treating a disease or condition, wherein the diseases, disorders, and/or condition is any one or more or  
5 combination of the following: cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia, psychosis, attention deficit disorder, attention deficit hyperactivity disorder, depression, anxiety, general anxiety disorder, post traumatic stress disorder, mood and  
10 affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems in general and associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including  
15 bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

In another aspect, the invention includes treating a mammal suffering from  
20 schizophrenia or psychosis by administering compounds of Formula I in conjunction with antipsychotic drugs (also called anti-psychotic agents). The compounds of the present invention and the antipsychotic drugs can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of the present invention and the antipsychotic drugs can be incorporated into a single  
25 pharmaceutical composition. Alternatively, two separate compositions, i.e., one containing compounds of the present invention and the other containing antipsychotic drugs, can be administered simultaneously.

In another aspect, the invention includes methods of treating a mammal suffering from schizophrenia or psychosis by administering compounds of Formula I  
30 in conjunction with antipsychotic drugs. The compounds of Formula I and the antipsychotic drugs can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of Formula I and the antipsychotic drugs can be incorporated into a single pharmaceutical composition. Alternatively,

two separate compositions, i.e., one containing compounds of Formula I and the other containing antipsychotic drugs, can be administered simultaneously.

The core molecule is the Azabicyclo-carboxamide-W:



5 Therefore, a bond indirectly attached to the core molecule would be the bond attached between the substituent and W of the core molecule, e.g, between the oxygen of -O-R<sub>7</sub> and W.

Abbreviations which are well known to one of ordinary skill in the art may be used (e.g., "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" or "hr" for hour or  
10 hours, min for minute or minutes, and "rt" or "RT" for room temperature).

All temperatures are in degrees Centigrade.

Room temperature is within the range of 15-25 degrees Celsius.

AChR refers to acetylcholine receptor.

nAChR refers to nicotinic acetylcholine receptor.

15 Pre-senile dementia is also known as mild cognitive impairment.

5HT<sub>3</sub>R refers to the serotonin-type 3 receptor.

$\alpha$ -btx refers to  $\alpha$ -bungarotoxin.

FLIPR refers to a device marketed by Molecular Devices, Inc. designed to precisely measure cellular fluorescence in a high throughput whole-cell assay.

20 (Schroeder et. al., *J. Biomolecular Screening*, 1(2), p 75-80, 1996).

TLC refers to thin-layer chromatography.

HPLC refers to high pressure liquid chromatography.

MeOH refers to methanol.

EtOH refers to ethanol.

25 IPA refers to isopropyl alcohol.

THF refers to tetrahydrofuran.

DMSO refers to dimethylsulfoxide.

DMF refers to *N,N*-dimethylformamide.

EtOAc refers to ethyl acetate.

30 TMS refers to tetramethylsilane.

TEA refers to triethylamine.

DIEA refers to *N,N*-diisopropylethylamine.

MLA refers to methyllycaconitine.

Ether refers to diethyl ether.

HATU refers to O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium  
5 hexafluorophosphate.

DBU refers to 1,8-diazobicyclo[5.4.0]undec-7-one.

CDI refers to carbonyl diimidazole.

NMO refers to *N*-methylmorpholine-*N*-oxide.

TPAP refers to tetrapropylammonium perruthenate.

10 Halogen is F, Cl, Br, or I.

Halogenated alkyl is used interchangeably with haloalkyl.

Lower halogenated alkyl is used interchangeably with lower haloalkyl.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon  
15 atoms in the moiety, i.e., the prefix C<sub>i-j</sub> indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C<sub>1-6</sub> alkyl refers to alkyl of one to six carbon atoms.

Non-inclusive examples of heteroaryl compounds that fall within the definition of R<sub>7</sub> and R<sub>9</sub> include, but are not limited to, thienyl, pyridyl, thiazolyl,  
20 pyrazinyl, pyrimidyl, imidazolyl, furanyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, pyrrolyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, and furazanyl.

Non-inclusive examples of heterocycloalkyl include, but are not limited to, tetrahydrofurano, tetrahydropyrano, morpholino, pyrrolidino, piperidino, piperazine,  
25 azetidino, azetidinono, oxindolo, dihydroimidazolo, and pyrrolidinono.

Mammal denotes human and other mammals.

Brine refers to an aqueous saturated sodium chloride solution.

Equ means molar equivalents.

IR refers to infrared spectroscopy.

30 Lv refers to leaving groups within a molecule, including Cl, OH, or mixed anhydride.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm ( $\delta$ ) downfield from TMS.



MS refers to mass spectrometry expressed as m/e or mass/charge unit. HRMS refers to high resolution mass spectrometry expressed as m/e or mass/charge unit.  $[M+H]^+$  refers to an ion composed of the parent plus a proton.  $[M-H]^-$  refers to an ion composed of the parent minus a proton.  $[M+Na]^+$  refers to an ion composed of the parent plus a sodium ion.  $[M+K]^+$  refers to an ion composed of the parent plus a potassium ion. EI refers to electron impact. ESI refers to electrospray ionization. CI refers to chemical ionization. FAB refers to fast atom bombardment.

Amino protecting group includes, but is not limited to, carbobenzyloxy (CBz), *tert* butoxy carbonyl (BOC) and the like. Examples of other suitable amino protecting groups are known to person skilled in the art and can be found in "Protective Groups in Organic synthesis," 3rd Edition, authored by Theodora Greene and Peter Wuts.

Compounds of the present invention may be in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases, and salts prepared from inorganic acids, and organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, ferric, ferrous, lithium, magnesium, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, such as arginine, betaine, caffeine, choline, N, N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and the like. Salts derived from inorganic acids include salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, phosphorous acid and the like. Salts derived from pharmaceutically acceptable organic non-toxic acids include salts of C<sub>1-6</sub> alkyl carboxylic acids, di-carboxylic acids, and tri-carboxylic acids such as acetic acid, propionic acid, fumaric acid, succinic acid, tartaric acid, maleic acid, adipic acid, and citric acid, and aryl and alkyl sulfonic acids such as toluene sulfonic acids and the like.

By the term "effective amount" of a compound as provided herein is meant a nontoxic but sufficient amount of the compound(s) to provide the desired effect. As pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease that is being treated, the particular compound(s) used, the mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount may be determined by one of ordinary skill in the art using only routine experimentation.

The amount of therapeutically effective compound(s) that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound(s) employed, and thus may vary widely. The compositions contain well known carriers and excipients in addition to a therapeutically effective amount of compounds of Formula I. The pharmaceutical compositions may contain active ingredient in the range of about 0.001 to 100 mg/kg/day for an adult, preferably in the range of about 0.1 to 50 mg/kg/day for an adult. A total daily dose of about 1 to 1000 mg of active ingredient may be appropriate for an adult. The daily dose can be administered in one to four doses per day.

In addition to the compound(s) of Formula I, the composition for therapeutic use may also comprise one or more non-toxic, pharmaceutically acceptable carrier materials or excipients. The term "carrier" material or "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier and/or diluent and/or adjuvant, or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. Acceptable excipients include lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc,

stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose, or other methods known to those skilled in the art. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. If desired, other active ingredients may be included in the composition.

10 In addition to the oral dosing, noted above, the compositions of the present invention may be administered by any suitable route, in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compositions may, for example, be administered parenterally, e.g., intravascularly, intraperitoneally, subcutaneously, or intramuscularly. For parenteral administration, saline solution, dextrose solution, or water may be used as a suitable carrier. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration.

15 20 The compounds may be dissolved in water, polyethylene glycol, propylene glycol, EtOH, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

The serotonin type 3 receptor (5HT<sub>3</sub>R) is a member of a superfamily of ligand-gated ion channels, which includes the muscle and neuronal nAChR, the glycine receptor, and the  $\gamma$ -aminobutyric acid type A receptor. Like the other members of this receptor superfamily, the 5HT<sub>3</sub>R exhibits a large degree of sequence homology with  $\alpha 7$  nAChR but functionally the two ligand-gated ion channels are very different. For example,  $\alpha 7$  nAChR is rapidly inactivated, is highly permeable to calcium and is activated by acetylcholine and nicotine. On the other hand, 5HT<sub>3</sub>R is inactivated slowly, is relatively impermeable to calcium and is activated by serotonin. These experiments suggest that the  $\alpha 7$  nAChR and 5HT<sub>3</sub>R proteins have some degree of homology, but function very differently. Indeed the pharmacology of the channels is

25 30

very different. For example, Ondansetron, a highly selective 5HT<sub>3</sub>R antagonist, has little activity at the  $\alpha 7$  nAChR. The converse is also true. For example, GTS-21, a highly selective  $\alpha 7$  nAChR agonist, has little activity at the 5HT<sub>3</sub>R.

$\alpha 7$  nAChR is a ligand-gated Ca<sup>++</sup> channel formed by a homopentamer of  $\alpha 7$  subunits. Previous studies have established that  $\alpha$ -bungarotoxin ( $\alpha$ -btx) binds selectively to this homopentameric,  $\alpha 7$  nAChR subtype, and that  $\alpha 7$  nAChR has a high affinity binding site for both  $\alpha$ -btx and methyllycaconitine (MLA).  $\alpha 7$  nAChR is expressed at high levels in the hippocampus, ventral tegmental area and ascending cholinergic projections from nucleus basalis to thalamocortical areas.  $\alpha 7$  nAChR agonists increase neurotransmitter release, and increase cognition, arousal, attention, learning and memory.

Data from human and animal pharmacological studies establish that nicotinic cholinergic neuronal pathways control many important aspects of cognitive function including attention, learning and memory (Levin, E.D., *Psychopharmacology*, 108:417-31, 1992; Levin, E.D. and Simon B.B., *Psychopharmacology*, 138:217-30, 1998). For example, it is well known that nicotine increases cognition and attention in humans. ABT-418, a compound that activates  $\alpha 4\beta 2$  and  $\alpha 7$  nAChR, improves cognition and attention in clinical trials of Alzheimer's disease and attention-deficit disorders (Potter, A. et. al., *Psychopharmacology (Berl)*, 142(4):334-42, Mar. 1999; Wilens, T. E. et. al., *Am. J. Psychiatry*, 156(12):1931-7, Dec. 1999). It is also clear that nicotine and selective but weak  $\alpha 7$  nAChR agonists increase cognition and attention in rodents and non-human primates.

Schizophrenia is a complex multifactorial illness caused by genetic and non-genetic risk factors that produce a constellation of positive and negative symptoms. The positive symptoms include delusions and hallucinations and the negative symptoms include deficits in affect, attention, cognition and information processing. No single biological element has emerged as a dominant pathogenic factor in this disease. Indeed, it is likely that schizophrenia is a syndrome that is produced by the combination of many low penetrance risk factors. Pharmacological studies established that dopamine receptor antagonists are efficacious in treating the overt psychotic features (positive symptoms) of schizophrenia such as hallucinations and delusions. Clozapine, an "atypical" antipsychotic drug, is novel because it is effective in treating both the positive and some of the negative symptoms of this disease.

Clozapine's utility as a drug is greatly limited because continued use leads to an increased risk of agranulocytosis and seizure. No other antipsychotic drug is effective in treating the negative symptoms of schizophrenia. This is significant because the restoration of cognitive functioning is the best predictor of a successful clinical and functional outcome of schizophrenic patients (Green, M.F., *Am J Psychiatry*, 153:321-30, 1996). By extension, it is clear that better drugs are needed to treat the cognitive disorders of schizophrenia in order to restore a better state of mental health to patients with this disorder.

One aspect of the cognitive deficit of schizophrenia can be measured by using the auditory event-related potential (P50) test of sensory gating. In this test, electroencephalographic (EEG) recordings of neuronal activity of the hippocampus are used to measure the subject's response to a series of auditory "clicks" (Adler, L.E. et. al., *Biol. Psychiatry*, 46:8-18, 1999). Normal individuals respond to the first click with greater degree than to the second click. In general, schizophrenics and schizotypal patients respond to both clicks nearly the same (Cullum, C.M. et. al., *Schizophr. Res.*, 10:131-41, 1993). These data reflect a schizophrenic's inability to "filter" or ignore unimportant information. The sensory gating deficit appears to be one of the key pathological features of this disease (Cadenhead, K.S. et. al., *Am. J. Psychiatry*, 157:55-9, 2000). Multiple studies show that nicotine normalizes the sensory deficit of schizophrenia (Adler, L.E. et. al., *Am. J. Psychiatry*, 150:1856-61, 1993). Pharmacological studies indicate that nicotine's effect on sensory gating is via the  $\alpha 7$  nAChR (Adler, L.E. et. al., *Schizophr. Bull.*, 24:189-202, 1998). Indeed, the biochemical data indicate that schizophrenics have 50% fewer of  $\alpha 7$  nAChR receptors in the hippocampus, thus giving a rationale to partial loss of  $\alpha 7$  nAChR functionality (Freedman, R. et. al., *Biol. Psychiatry*, 38:22-33, 1995). Interestingly, genetic data indicate that a polymorphism in the promoter region of the  $\alpha 7$  nAChR gene is strongly associated with the sensory gating deficit in schizophrenia (Freedman, R. et. al., *Proc. Nat'l Acad. Sci. USA*, 94(2):587-92, 1997; Myles-Worsley, M. et. al., *Am. J. Med. Genet*, 88(5):544-50, 1999). To date, no mutation in the coding region of the  $\alpha 7$  nAChR has been identified. Thus, schizophrenics express the same  $\alpha 7$  nAChR as non-schizophrenics.

Selective  $\alpha 7$  nAChR agonists may be found using a functional assay on FLIPR (see WO 00/73431 A2). FLIPR is designed to read the fluorescent signal from each

well of a 96 or 384 well plate as fast as twice a second for up to 30 minutes. This assay may be used to accurately measure the functional pharmacology of  $\alpha 7$  nAChR and 5HT<sub>3</sub>R. To conduct such an assay, one uses cell lines that expressed functional forms of the  $\alpha 7$  nAChR using the  $\alpha 7/5$ -HT<sub>3</sub> channel as the drug target and cell lines  
5 that expressed functional 5HT<sub>3</sub>R. In both cases, the ligand-gated ion channel was expressed in SH-EP1 cells. Both ion channels can produce robust signal in the FLIPR assay.

The compounds of the present invention are  $\alpha 7$  nAChR agonists and may be used to treat a wide variety of diseases. For example, they may be used in treating  
10 schizophrenia, or psychosis.

Schizophrenia is a disease having multiple aspects. Currently available drugs are generally aimed at controlling the positive aspects of schizophrenia, such as delusions. One drug, Clozapine, is aimed at a broader spectrum of symptoms associated with schizophrenia. This drug has many side effects and is thus not  
15 suitable for many patients. Thus, there is a need for a drug to treat the cognitive and attention deficits associated with schizophrenia. Similarly, there is a need for a drug to treat the cognitive and attention deficits associated with schizoaffective disorders, or similar symptoms found in the relatives of schizophrenic patients.

Psychosis is a mental disorder characterized by gross impairment in the  
20 patient's perception of reality. The patient may suffer from delusions, and hallucinations, and may be incoherent in speech. His behavior may be agitated and is often incomprehensible to those around him. In the past, the term psychosis has been applied to many conditions that do not meet the stricter definition given above. For example, mood disorders were named as psychoses.

25 There are a variety of antipsychotic drugs. The conventional antipsychotic drugs include Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Perphenazine, Pimozide, Thioridazine, Thiothixene, and Trifluoperazine. These drugs all have an affinity for the dopamine 2 receptor.

These conventional antipsychotic drugs have several side effects, including  
30 sedation, weight gain, tremors, elevated prolactin levels, akathisia (motor restlessness), dystonia and muscle stiffness. These drugs may also cause tardive dyskinesia. Unfortunately, only about 70% of patients with schizophrenia respond to

conventional antipsychotic drugs. For these patients, atypical antipsychotic drugs are available.

Atypical antipsychotic drugs generally are able to alleviate positive symptoms of psychosis while also improving negative symptoms of the psychosis to a greater degree than conventional antipsychotics. These drugs may improve neurocognitive deficits. Extrapyramidal (motor) side effects are not as likely to occur with the atypical antipsychotic drugs, and thus, these atypical antipsychotic drugs have a lower risk of producing tardive dyskinesia. Finally these atypical antipsychotic drugs cause little or no elevation of prolactin. Unfortunately, these drugs are not free of side effects. Although these drugs each produce different side effects, as a group the side effects include: agranulocytosis; increased risk of seizures, weight gain, somnolence, dizziness, tachycardia, decreased ejaculatory volume, and mild prolongation of QTc interval.

In a combination therapy to treat multiple symptoms of diseases including schizophrenia, the compounds of Formula I and the anti-psychotic drugs can be administered simultaneously or at separate intervals. When administered simultaneously the compounds of Formula I and the anti-psychotic drugs can be incorporated into a single pharmaceutical composition, e.g., a pharmaceutical combination therapy composition. Alternatively, two separate compositions, i.e., one containing compounds of Formula I and the other containing anti-psychotic drugs, can be administered simultaneously. Examples of anti-psychotic drugs, in addition to those listed above, include, but are not limited to, Thorazine, Mellaril, Trilafon, Navane, Stelazine, Permitil, Prolixin, Risperdal, Zyprexa, Seroquel, ZELDOX, Acetophenazine, Carphenazine, Chlorprothixene, Droperidol, Loxapine, Mesoridazine, Molindone, Ondansetron, Pimozide, Prochlorperazine, and Promazine.

A pharmaceutical combination therapy composition can include therapeutically effective amounts of the compounds of Formula I, noted above, and a therapeutically effective amount of anti-psychotic drugs. These compositions may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered rectally, topically, orally, sublingually, or parenterally and maybe formulated as sustained relief dosage forms and the like.

When separately administered, therapeutically effective amounts of compositions containing compounds of Formula I and anti-psychotic drugs are administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. A therapeutically effective interval is a period of time beginning when one of either (a) the compounds of Formula I, or (b) the anti-psychotic drugs is administered to a human and ending at the limit of the beneficial effect in the treatment of schizophrenia or psychosis of the combination of (a) and (b). The methods of administration of the compounds of Formula I and the anti-psychotic drugs may vary. Thus, either agent or both agents may be administered rectally, topically, orally, sublingually, or parenterally.

As discussed, the compounds of the present invention are  $\alpha 7$  nAChR agonists. Therefore, as another aspect of the present invention, the compounds of the present invention may be used to treat a variety of diseases including cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (also known as mild cognitive impairment), and senile dementia.

Alzheimer's disease has many aspects, including cognitive and attention deficits. Currently, these deficits are treated with cholinesterase inhibitors. These inhibitors slow the break down of acetylcholine, and thereby provide a general nonspecific increase in the activity of the cholinergic nervous system. Since the drugs are nonspecific, they have a wide variety of side effects. Thus, there is a need for a drug that stimulates a portion of the cholinergic pathways and thereby provides improvement in the cognitive and attention deficits associated with Alzheimer's disease without the side effects created by nonspecific stimulation of the cholinergic pathways.

Neurodegeneration is a common problem associated with diseases such as Alzheimer's disease. While the current drugs treat some of the symptoms of this disease, they do not control the underlying pathology of the disease. Accordingly, it would be desirable to provide a drug that can slow the progress of Alzheimer's disease.



Pre-senile dementia (mild cognitive impairment) concerns memory impairment rather than attention deficit problems and otherwise unimpaired cognitive functioning. Mild cognitive impairment is distinguished from senile dementia in that mild cognitive impairment involves a more persistent and troublesome problem of memory loss for the age of the patient. There currently is no medication specifically identified for treatment of mild cognitive impairment, due somewhat to the newness of identifying the disease. Therefore, there is a need for a drug to treat the memory problems associated with mild cognitive impairment.

Senile dementia is not a single disease state. However, the conditions classified under this name frequently include cognitive and attention deficits. Generally, these deficits are not treated. Accordingly, there is a need for a drug that provides improvement in the cognitive and attention deficits associated with senile dementia.

As discussed, the compounds of the present invention are  $\alpha 7$  nAChR agonists. Therefore, yet other diseases to be treated with compounds of the present invention include treating the cognitive and attention deficits as well as the neurodegeneration associated with any one or more or combination of the following: attention deficit disorder, attention deficit hyperactivity disorder, depression, anxiety, general anxiety disorder, post traumatic stress disorder, mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

Attention deficit disorder is generally treated with methylphenidate, an amphetamine-like molecule that has some potential for abuse. Accordingly, it would be desirable to provide a drug that treats attention deficit disorder while having fewer side effects than the currently used drug.

Attention deficit hyperactivity disorder, otherwise known as ADHD, is a neurobehavioral disorder affecting 3-5% of all American children. ADHD concerns cognitive alone or both cognitive and behavioral actions by interfering with a person's ability to stay on a task and to exercise age-appropriate inhibition. Several types of ADHD exist: a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype. Treatment may include medications such as methylphenidate, dextroamphetamine, or pemoline, which act to decrease impulsivity and hyperactivity and to increase attention. No "cure" for ADHD currently exists. Children with the disorder seldom outgrow it; therefore, there is a need for appropriate medicaments.

Depression is a mood disorder of varying lengths of normally several months to more than two years and of varying degrees of feelings involving sadness, despair, and discouragement. The heterocyclic antidepressants (HCA's) are currently the largest class of antidepressants, but monoamine oxidase inhibitors (MAOI's) are used in particular types of depression. Common side effects from HCA's are sedation and weight gain. In elderly patients with organic brain disease, the side effects from HCA's can also include seizures and behavioral symptoms. The main side effects from using MAOI's occur from dietary and drug interactions. Therefore, agents with fewer side effects would be useful.

Anxiety disorders (disorders with prominent anxiety or phobic avoidance), represent an area of unmet medical needs in the treatment of psychiatric illness. See Diagnostic & Statistical Manual of Mental Disorders, IV (1994), pp 393-394, for various disease forms of anxiety.

General anxiety disorder (GAD) occurs when a person worries about things such as family, health, or work when there is no reason to worry and is unable not to worry. About 3 to 4% of the U.S. population has GAD during the course of a year. GAD most often strikes people in childhood or adolescence, but can begin in adulthood, too. It affects women more often than men. Currently, treatment involves cognitive-behavioral therapy, relaxation techniques, and biofeedback to control muscle tension and medications such as benzodiazepines, imipramine, and buspirone. These drugs are effective but all have side-effect liabilities. Therefore, there is a need of a pharmaceutical agent to address the symptoms with fewer side effects.

Anxiety also includes post-traumatic stress disorder (PTSD), which is a form of anxiety triggered by memories of a traumatic event that directly affected the patient or that the patient may have witnessed. The disorder commonly affects survivors of traumatic events including sexual assault, physical assault, war, torture, natural disasters, an automobile accident, an airplane crash, a hostage situation, or a death camp. The affliction also can affect rescue workers at an airplane crash or a mass shooting, someone who witnessed a tragic accident or someone who has unexpectedly lost a loved one. Treatment for PTSD includes cognitive-behavioral therapy, group psychotherapy, and medications such as Clonazepam, Lorazepam and selective serotonin-reuptake inhibitors such as Fluoxetine, Sertraline, Paroxetine, Citalopram and Fluvoxamine. These medications help control anxiety as well as depression. Various forms of exposure therapy (such as systemic desensitization and imaginal flooding) have all been used with PTSD patients. Exposure treatment for PTSD involves repeated reliving of the trauma, under controlled conditions, with the aim of facilitating the processing of the trauma. Therefore, there is a need for better pharmaceutical agents to treat post traumatic stress disorder.

Mood and affective disorders fall within a large group of diseases, including monopolar depression and bi-polar mood disorder. These diseases are treated with three major classes of compounds. The first group is the heterocyclic antidepressant (HCA's). This group includes the well-known tricyclic antidepressants. The second group of compounds used to treat mood disorders is the monoamine oxidase inhibitors (MAOI's) that are used in particular types of diseases. The third drug is lithium. Common side effects from HCA's are sedation and weight gain. In elderly patients with organic brain disease, the side effects of HCA's can also include seizures and behavioral symptoms. The main side effects from using MAOI's occur from dietary and drug interactions. Benign side effects from the use of lithium include, but are not limited to, weight gain, nausea, diarrhea, polyuria, polydipsia, and tremor. Toxic side effects from lithium can include persistent headache, mental confusion, and may reach seizures and cardiac arrhythmias. Therefore, agents with less side effects or interactions with food or other medications would be useful.

Borderline personality disorder, although not as well known as bipolar disorder, is more common. People having borderline personality disorder suffer from

a disorder of emotion regulation. Pharmaceutical agents are used to treat specific symptoms, such as depression or thinking distortions.

5 Acquired immune deficiency syndrome (AIDS) results from an infection with the human immunodeficiency virus (HIV). This virus attacks selected cells and impairs the proper function of the immune, nervous, and other systems. HIV infection can cause other problems such as, but not limited to, difficulties in thinking, otherwise known as AIDS dementia complex. Therefore, there is a need to drugs to relieve the confusion and mental decline of persons with AIDS.

10 Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, belongs to a class of disorders known as motor neuron diseases wherein specific nerve cells in the brain and spinal cord gradually degenerate to negatively affect the control of voluntary movement. Currently, there is no cure for amyotrophic lateral sclerosis although patients may receive treatment from some of their symptoms and although Riluzole has been shown to prolong the survival of patients. Therefore, there is a  
15 need for a pharmaceutical agent to treat this disease.

Traumatic brain injury occurs when the brain is damaged from a sudden physical assault on the head. Symptoms of the traumatic brain injury include confusion and other cognitive problems. Therefore, there is a need to address the symptoms of confusion and other cognitive problems.

20 Brain tumors are abnormal growths of tissue found inside of the skull. Symptoms of brain tumors include behavioral and cognitive problems. Surgery, radiation, and chemotherapy are used to treat the tumor, but other agents are necessary to address associated symptoms. Therefore, there is a need to address the symptoms of behavioral and cognitive problems.

25 Persons with Down's syndrome have in all or at least some of their cells an extra, critical portion of the number 21 chromosome. Adults who have Down's syndrome are known to be at risk for Alzheimer-type dementia. Currently, there is no proven treatment for Down's syndrome. Therefore, there is a need to address the dementia associated with Down's syndrome.

30 Genetically programmed degeneration of neurons in certain areas of the brain cause Huntington's disease. Early symptoms of Huntington's disease include mood swings, or trouble learning new things or remembering a fact. Most drugs used to treat the symptoms of Huntington's disease have side effects such as fatigue,

restlessness, or hyperexcitability. Currently, there is no treatment to stop or reverse the progression of Huntington's disease. Therefore, there is a need of a pharmaceutical agent to address the symptoms with fewer side effects.

5 Dementia with Lewy Bodies is a neurodegenerative disorder involving abnormal structures known as Lewy bodies found in certain areas of the brain. Symptoms of dementia with Lewy bodies include, but are not limited to, fluctuating cognitive impairment with episodic delirium. Currently, treatment concerns addressing the parkinsonian and psychiatric symptoms. However, medicine to control tremors or loss of muscle movement may actually accentuate the underlying disease of  
10 dementia with Lewy bodies. Therefore, there is a need of a pharmaceutical agent to treat dementia with Lewy bodies.

Parkinson's disease is a neurological disorder characterized by tremor, hypokinesia, and muscular rigidity. Currently, there is no treatment to stop the progression of the disease. Therefore, there is a need of a pharmaceutical agent to  
15 address Parkinson's.

Tardive dyskinesia is associated with the use of conventional antipsychotic drugs. This disease is characterized by involuntary movements most often manifested by puckering of the lips and tongue and/or writhing of the arms or legs. The incidence of tardive dyskinesia is about 5% per year of drug exposure among patients taking  
20 conventional antipsychotic drugs. In about 2% of persons with the disease, tardive dyskinesia is severely disfiguring. Currently, there is no generalized treatment for tardive dyskinesia. Furthermore, the removal of the effect-causing drugs is not always an option due to underlying problems. Therefore, there is a need for a pharmaceutical agent to address the symptoms of tardive dyskinesia.

25 Pick's disease results from a slowly progressive deterioration of social skills and changes in personality with the resulting symptoms being impairment of intellect, memory, and language. Common symptoms include memory loss, lack of spontaneity, difficulty in thinking or concentrating, and speech disturbances. Currently, there is no specific treatment or cure for Pick's disease but some symptoms  
30 can be treated with cholinergic and serotonin-boosting antidepressants. In addition, antipsychotic medications may alleviate symptoms in FTD patients who are experiencing delusions or hallucinations. Therefore, there is a need for a

pharmaceutical agent to treat the progressive deterioration of social skills and changes in personality and to address the symptoms with fewer side effects.

Dysregulation of food intake associated with eating disease, including bulimia nervosa and anorexia nervosa, involve neurophysiological pathways. Anorexia nervosa is hard to treat due to patients not entering or remaining in after entering programs. Currently, there is no effective treatment for persons suffering from severe anorexia nervosa. Cognitive behavioral therapy has helped patients suffering from bulimia nervosa; however, the response rate is only about 50% and current treatment does not adequately address emotional regulation. Therefore, there is a need for pharmaceutical agents to address neurophysiological problems underlying diseases of dysregulation of food intake.

Cigarette smoking has been recognized as a major public health problem for a long time. However, in spite of the public awareness of health hazard, the smoking habit remains extraordinarily persistent and difficult to break. There are many treatment methods available, and yet people continue to smoke. Administration of nicotine transdermally, or in a chewing gum base is common treatments. However, nicotine has a large number of actions in the body, and thus can have many side effects. It is clear that there is both a need and a demand of long standing for a convenient and relatively easy method for aiding smokers in reducing or eliminating cigarette consumption. A drug that could selectively stimulate only certain of the nicotinic receptors would be useful in smoke cessation programs.

Smoke cessation programs may involve oral dosing of the drug of choice. The drug may be in the form of tablets. However, it is preferred to administer the daily dose over the waking hours, by administration of a series of incremental doses during the day. The preferred method of such administration is a slowly dissolving lozenge, troche, or chewing gum, in which the drug is dispersed. Another drug in treating nicotine addiction is Zyban. This is not a nicotine replacement, as are the gum and patch. Rather, this works on other areas of the brain, and its effectiveness is to help control nicotine craving or thoughts about cigarette use in people trying to quit. Zyban is not very effective and effective drugs are needed to assist smokers in their desire to stop smoking. These drugs may be administered transdermally through the use of skin patches. In certain cases, the drugs may be administered by subcutaneous injection, especially if sustained release formulations are used.

Drug use and dependence is a complex phenomenon, which cannot be encapsulated within a single definition. Different drugs have different effects, and therefore different types of dependence. Drug dependence has two basic causes, that is, tolerance and physical dependence. Tolerance exists when the user must take progressively larger doses to produce the effect originally achieved with smaller doses. Physical dependence exists when the user has developed a state of physiologic adaptation to a drug, and there is a withdrawal (abstinence) syndrome when the drug is no longer taken. A withdrawal syndrome can occur either when the drug is discontinued or when an antagonist displaces the drug from its binding site on cell receptors, thereby counteracting its effect. Drug dependence does not always require physical dependence.

In addition drug dependence often involves psychological dependence, that is, a feeling of pleasure or satisfaction when taking the drug. These feelings lead the user to repeat the drug experience or to avoid the displeasure of being deprived of the drug. Drugs that produce strong physical dependence, such as nicotine, heroin and alcohol are often abused, and the pattern of dependence is difficult to break. Drugs that produce dependence act on the CNS and generally reduce anxiety and tension; produce elation, euphoria, or other pleasurable mood changes; provide the user feelings of increased mental and physical ability; or alter sensory perception in some pleasurable manner. Among the drugs that are commonly abused are ethyl alcohol, opioids, anxiolytics, hypnotics, cannabis (marijuana), cocaine, amphetamines, and hallucinogens. The current treatment for drug-addicted people often involves a combination of behavioral therapies and medications. Medications, such as methadone or LAAM (levo-alpha-acetyl-methadol), are effective in suppressing the withdrawal symptoms and drug craving associated with narcotic addiction, thus reducing illicit drug use and improving the chances of the individual remaining in treatment. The primary medically assisted withdrawal method for narcotic addiction is to switch the patient to a comparable drug that produces milder withdrawal symptoms, and then gradually taper off the substitute medication. The medication used most often is methadone, taken orally once a day. Patients are started on the lowest dose that prevents the more severe signs of withdrawal and then the dose is gradually reduced. Substitutes can be used also for withdrawal from sedatives.

Patients can be switched to long-acting sedatives, such as diazepam or phenobarbital, which are then gradually reduced.

Gilles de la Tourette's Syndrome is an inherited neurological disorder. The disorder is characterized by uncontrollable vocal sounds called tics and involuntary movements. The symptoms generally manifest in an individual before the person is 18 years of age. The movement disorder may begin with simple tics that progress to multiple complex tics, including respiratory and vocal ones. Vocal tics may begin as grunting or barking noises and evolve into compulsive utterances. Coprolalia (involuntary scatologic utterances) occurs in 50% of patients. Severe tics and coprolalia may be physically and socially disabling. Tics tend to be more complex than myoclonus, but less flowing than choreic movements, from which they must be differentiated. The patient may voluntarily suppress them for seconds or minutes.

Currently simple tics are often treated with benzodiazepines. For simple and complex tics, Clonidine may be used. Long-term use of Clonidine does not cause tardive dyskinesia; its limiting adverse effect is hypotension. In more severe cases, antipsychotics, such as Haloperidol may be required, but side effects of dysphoria, parkinsonism, akathisia, and tardive dyskinesia may limit use of such antipsychotics. There is a need for safe and effective methods for treating this syndrome.

Age-related macular degeneration (AMD) is a common eye disease of the macula which is a tiny area in the retina that helps produce sharp, central vision required for "straight ahead" activities that include reading and driving. Persons with AMD lose their clear, central vision. AMD takes two forms: wet and dry. In dry AMD, there is a slow breakdown of light-sensing cells in the macula. There currently is no cure for dry AMD. In wet AMD, new, fragile blood vessels growing beneath the macula as dry AMD worsens and these vessels often leak blood and fluid to cause rapid damage to the macula quickly leading to the loss of central vision. Laser surgery can treat some cases of wet AMD. Therefore, there is a need of a pharmaceutical agent to address AMD.

Glaucoma is within a group of diseases occurs from an increase in intraocular pressure causing pathological changes in the optical disk and negatively affects the field of vision. Medicaments to treat glaucoma either decrease the amount of fluid entering the eye or increase drainage of fluids from the eye in order to decrease intraocular pressure. However, current drugs have drawbacks such as not working



over time or causing side effects so the eye-care professional has to either prescribe other drugs or modify the prescription of the drug being used. There is a need for safe and effective methods for treating problems manifesting into glaucoma.

Ischemic periods in glaucoma cause release of excitotoxic amino acids and stimulate inducible form of nitric oxide synthase (iNOS) leading to neurodegeneration. Alpha 7 nicotinic agonists may stimulate the release of inhibitory amino acids such as GABA which will dampen hyperexcitability. Alpha 7 nicotinic agonists are also directly neuroprotective on neuronal cell bodies. Thus alpha 7 nicotinic agonists have the potential to be neuroprotective in glaucoma.

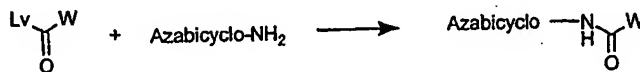
Persons afflicted with pain often have what is referred to as the "terrible triad" of suffering from the pain, resulting in sleeplessness and sadness, all of which are hard on the afflicted individual and that individual's family. Pain can manifest itself in various forms, including, but not limited to, headaches of all severity, back pain, neurogenic, and pain from other ailments such as arthritis and cancer from its existence or from therapy to irradiate it. Pain can be either chronic (persistent pain for months or years) or acute (short-lived, immediate pain to inform the person of possible injury and need of treatment). Persons suffering from pain respond differently to individual therapies with varying degrees of success. There is a need for safe and effective methods for treating pain.

Finally, the compounds of the present invention may be used in combination therapy with typical and atypical anti-psychotic drugs (also called an anti-psychotic agent). All compounds within the present invention are useful for and may also be used in combination with each other to prepare pharmaceutical compositions. Such combination therapy lowers the effective dose of the anti-psychotic drug and thereby reduces the side effects of the anti-psychotic drugs. Some typical anti-psychotic drugs that may be used in the practice of the invention include Haldol. Some atypical anti-psychotic drugs include Ziprasidone, Olanzapine, Risperidone, and Quetiapine.

Compounds of Formula I can be prepared as shown in Scheme 1. The key step in the preparation of this class of compounds is the coupling of an amino-azabicyclic moiety with the requisite acid chloride ( $L_v = Cl$ ), mixed anhydride (e.g.,  $L_v =$  diphenyl phosphoryl, Bis(2-oxo-3-oxazolidinyl)phosphinyl, or acyloxy of the general formula of  $O-C(O)-R_{L_v}$ , where  $R_{L_v}$  includes phenyl or *t*-butyl), or carboxylic acid ( $L_v = OH$ ) in the presence of an activating agent. Suitable activating reagents are well

known in the art, for examples see Kiso, Y., Yajima, H. "Peptides" pp. 39-91, San Diego, CA, Academic Press, (1995), and include, but are not limited to, agents such as carbodiimides, phosphonium and uronium salts (such as HATU).

Scheme 1



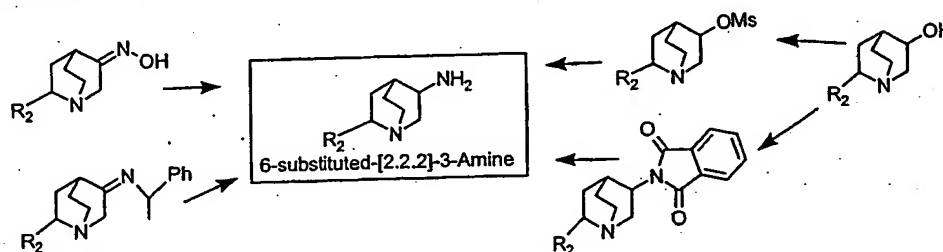
Generally, the acid is activated using HATU or is converted to the acyl azide by using DPPA or is converted into a mixed anhydride by treatment with bis (2-oxo-3-oxazolidinyl) phosphinic chloride in the presence of TEA with  $\text{CH}_2\text{Cl}_2$  or  $\text{CHCl}_3$  as the solvent. In the case where  $\text{R}_4$  is *tert*-butyloxycarbonyl (where Azabicyclo is VII), deprotection of the 7-aza group can be conveniently accomplished under acidic conditions in a suitable solvent such as methanol.

Preferably, for Azabicyclo III, Azabicyclo IV, and Azabicyclo VII, the acid is converted into a mixed anhydride by treatment with bis (2-oxo-3-oxazolidinyl) phosphinic chloride in the presence of TEA with  $\text{CH}_2\text{Cl}_2$  or  $\text{CHCl}_3$  as the solvent. The resulting anhydride solution is directly reacted with the appropriate Azabicyclo moiety added neat or using DMF or aqueous DMF as solvent. In some cases, the ester (Lv being OMe or OEt) may be reacted directly with the amine in refluxing methanol or ethanol to give the compounds of Formula I.

The appropriate amine is reacted with TEA if the amine is in the form of an acid salt and added to a solution of the appropriate anhydride or azide to give the desired final compounds. In some cases, the ester (Lv being OMe or OEt) may be reacted directly with the amine in refluxing methanol or ethanol to give the compounds of Formula I.

One of ordinary skill in the art will recognize that the methods described for the reaction of the unsubstituted 3-aminoquinuclidine ( $\text{R}_2$  is H) are equally applicable to substituted compounds ( $\text{R}_2$  is other than H). Certain 6-substituted-[2.2.2]-3-amines (Azabicyclo I) are known in the art. The preparation of compounds where  $\text{R}_2$  is at C-6 of the quinuclidine and is other than H is described in *Acta Pol. Pharm.* 1981, 179. Certain 2-substituted-[2.2.2]-3-amines (Azabicyclo I) are known in the art. The preparation of compounds where  $\text{R}_2$  is at C-2 of the quinuclidine and is other than H is described in *J. Med. Chem.* 1975, 18, 587.

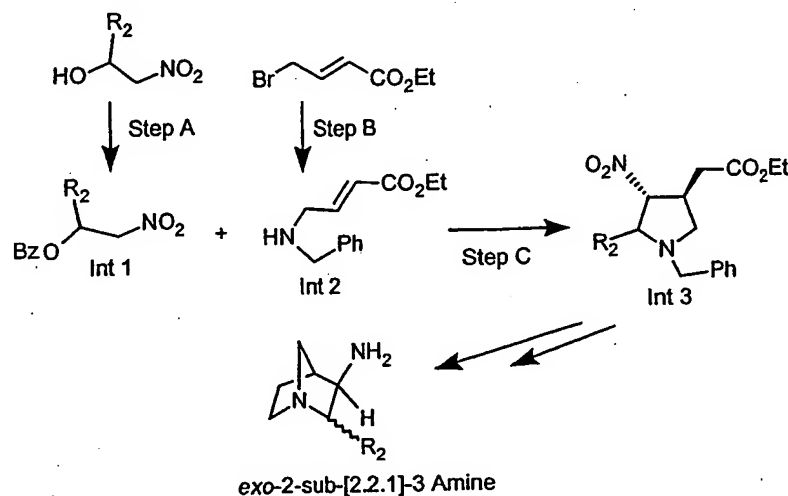
Alternatively, there are several methods by which the amine precursor for Azabicyclo I where  $R_2$  is other than H can be obtained. Although the scheme depicted below is for compounds where  $R_2$  is at the C-6 position of the quinuclidine, one of ordinary skill in the art would be able to obtain the quinuclidine with substitution at C-2 also. The substituted-[2.2.2]-3-amine can be prepared by reduction of an oxime or an imine of the corresponding substituted-3-quinuclidinone by methods known to one of ordinary skill in the art (see *J. Labelled Compds. Radiopharm.* 1995, 53; *J. Med. Chem.* 1998, 988; *Synth. Commun.* 1992, 1895; *Synth. Commun.* 1996, 2009). Alternatively, the substituted-[2.2.2]-3-amine can be prepared from a substituted-3-hydroxyquinuclidine by Mitsunobu reaction followed by deprotection as described in *Synth. Commun.* 1995, 1895. Alternatively, the substituted-[2.2.2]-3-amine can be prepared by conversion of a substituted-3-hydroxyquinuclidine into the corresponding mesylate or tosylate, followed by displacement with sodium azide and reduction as described in *J. Med. Chem.* 1975, 587.



The 2-substituted-3-quinuclidinones, where  $R_2$  is substituted alkyl, cycloalkyl, or can be prepared by known procedures (see *Tett. Lett.* 1972, 1015; *J. Am. Chem. Soc.* 1994, 1278; *J. Am. Chem. Soc.* 1989, 4548; *Tetrahedron*, 2000, 1139). The 2-substituted-3-quinuclidinones, where  $R_2$  is aryl, can be prepared by palladium catalyzed arylation as described in *J. Am. Chem. Soc.* 1999, 1473 and *J. Am. Chem. Soc.* 2000, 1360. The 6-substituted-3-quinuclidinones can be prepared by known procedures (see *J. Gen. Chem. Russia* 1963, 3791, *J. Chem. Soc. Perkin Trans. I* 1991, 409, *J. Org. Chem.* 2000, 3982).

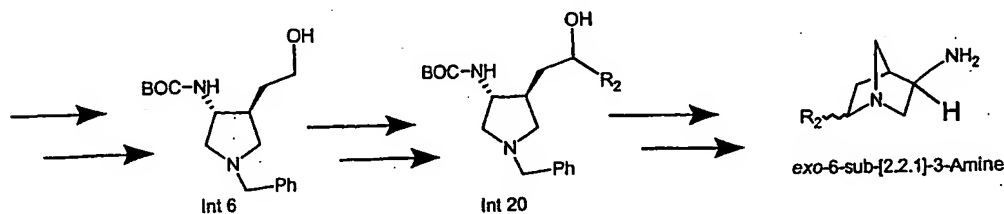
One of ordinary skill in the art will recognize that the methods described for the reaction of the unsubstituted 3-amino-1-azabicyclo[2.2.1]heptane ( $R_2=H$ ) are equally applicable to substituted compounds ( $R_2 \neq H$ ). For where Azabicyclo II has substitution at C-2, compounds can be prepared from appropriately substituted nitro alcohols using procedures described in *Tetrahedron* (1997), 53, p. 11121 as shown below. Methods to synthesize nitro alcohols are well known in the art (see *J. Am.*

*Chem. Soc.* (1947), 69, p 2608). The scheme below is a modification of the synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt, described in detail herein, to show how to obtain these amine precursors. The desired salt can be made using standard procedures.



5

For Azabicyclo II where  $R_2$  is other than H at the C-6 position, compounds can also be prepared by modification of intermediates described in the synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt, described in detail herein. For example, Int 6 can be oxidized to the aldehyde and treated with an organometallic reagent to provide Int 20 using procedures described in *Tetrahedron* (1999), 55, p 13899. Int 20 can be converted into the amine using methods described for the synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt. Once the amine is obtained, the desired salt can be made using standard procedures.



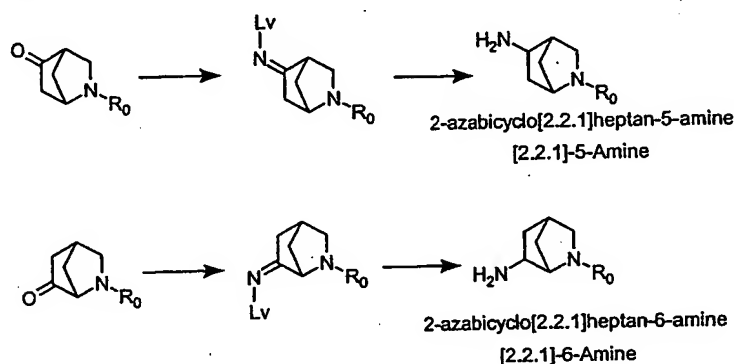
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The schemes used are for making *exo*-3-amino-1-azabicyclo[2.2.1]heptane. However, the modifications discussed are applicable to make the *endo* isomer also.

One of ordinary skill in the art will also recognize that the methods described for the reaction of the unsubstituted 1-azabicyclo[3.2.1]octan-3-amine or 1-azabicyclo[3.2.2]nonan-3-amine ( $R_2=H$ ) are equally applicable to substituted compounds ( $R_2 \neq H$ ). The  $R_2$  substituent may be introduced as known to one skilled

in the art through standard alkylation chemistry. Exposure of 1-azabicyclo[3.2.1]octan-3-one or 1-azabicyclo[3.2.2]nonan-3-one to a hindered base such as LDA (lithium diisopropylamide) in a solvent such as THF or ether between 0°C to -78°C followed by the addition of an alkylating agent ( $R_2Lv$ , where  $Lv = Cl, Br, I, OTs$ , etc.) will, after being allowed to warm to about 0°C to rt followed by an aqueous workup, provide the desired compound as a mixture of isomers. Chromatographic resolution (flash, HPLC, or chiral HPLC) will provide the desired purified alkylated ketones. From there, formation of the oxime and subsequent reduction will provide the desired stereoisomers.

***N*-(2-azabicyclo[2.2.1]hept)-5-amine and 6-amine:**



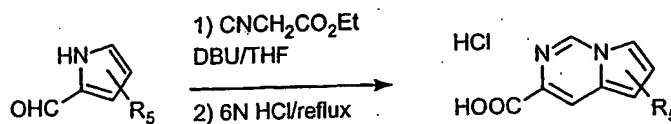
where  $Lv$  can be  $-CH_2Ph$ ,  $-CH(Me)Ph$ ,  $-OH$ ,  $-OMe$ , or  $-OCH_2Ph$ .

The respective amine precursors for Azabicyclo V and Azabicyclo VI can be prepared by reduction of an oxime or an imine of the corresponding *N*-2-azabicyclo[2.2.1]-heptanone by methods known to one skilled in the art (see *J. Labelled Compds. Radiopharm.*, 53-60 (1995), *J. Med. Chem.* 988-995, (1998), *Synth. Commun.* 1895-1911 (1992), *Synth. Commun.* 2009-2015 (1996)). The oximes can be prepared by treatment of the *N*-2-azabicyclo[2.2.1]heptanones with hydroxylamine hydrochloride in the presence of a base. The imines can be prepared by treatment of the *N*-2-azabicyclo[2.2.1]-heptanones with a primary amine under dehydrating conditions. The *N*-2-azabicyclo[2.2.1]heptanones can be prepared by known procedures (see *Tet. Lett.* 1419-1422 (1999), *J. Med. Chem.* 2184-2191 (1992), *J. Med. Chem.* 706-720 (2000), *J. Org. Chem.*, 4602-4616 (1995)).

It will be apparent to those skilled in the art that the requisite carboxylic acids can be synthesized by known procedures, many are described herein. For example, 3-(pyrrolo[1,2-*c*]pyrimidine)carboxylic acid can be synthesized from the corresponding

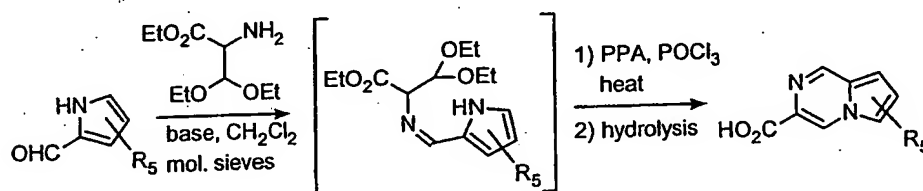
pyrrole-2-carboxaldehyde by reaction with an isocyanoacetate in the presence of base as described in *J. Org. Chem.* **1999**, *64*, 7788 and *J. Org. Chem.* **1976**, *41*, 1482 or by methods described in *Liebigs Ann. Chem.* **1987**, 491. Scheme 2 depicts this transformation.

Scheme 2



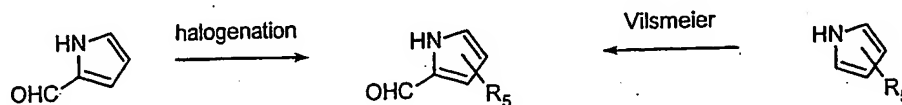
The pyrrolo[1,2-a]pyrazine acid fragment can be prepared using the methods shown in Scheme 3. The ester intermediate can be prepared using methods described in Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 8139-46, whereby the requisite pyrrole-2-carboxaldehyde is reacted with aminoester diethylacetal to form the imine. The imine can then be cyclized under acidic conditions to afford the desired bicyclic core. The resulting ester can be hydrolyzed under typical hydrolysis procedures well known in the art to afford the requisite pyrrolo[1,2-a]pyrazine acids.

Scheme 3



The pyrrole-2-carboxaldehydes can be obtained from commercial sources or can be synthesized by known procedures. For example, pyrrole-2-carboxaldehyde can be converted into 4-halo, 5-halo and 4,5-dihalopyrrole-2-carboxaldehydes as described in *Bull. Soc. Chim. Fr.* **1973**, 351. See Examples 12-22. Alternatively, substituted pyrroles can be converted into pyrrole carboxaldehydes by Vilsmeier formylation using procedures well known in the art (see *J. Het. Chem.* **1991**, *28*, 2053, *Synth. Commun.* **1994**, *24*, 1389 or *Synthesis*, **1995**, 1480. Scheme 4 depicts these transformations.

Scheme 4



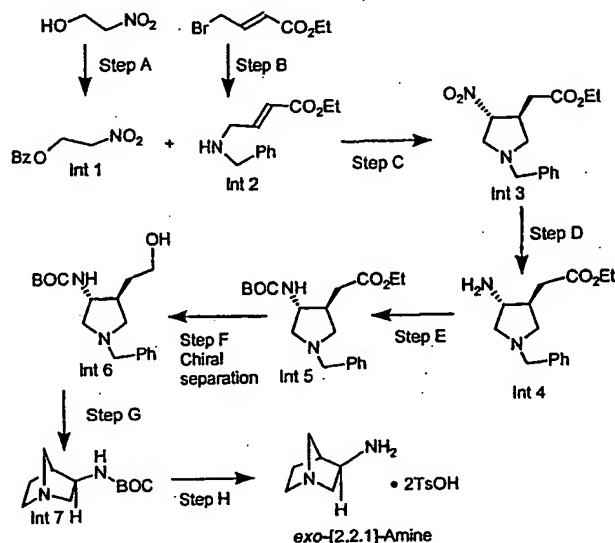
## AMINES

Preparation of *N*-(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (2*S*-methyl-2.2.2-Amine): See, e.g., US 20020042428 A1.

5

## Preparation of the 1-azabicyclo-2.2.1 Amines:

Synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt (*exo*-[2.2.1]-Amine):



## 10 Step A. Preparation of 2-(benzoyloxy)-1-nitroethane (Int 1).

Benzoyl chloride (14.9 mL, 128 mmol) is added to a stirred solution of nitroethanol (9.2 mL, 128 mmol) in dry benzene (120 mL). The solution is refluxed for 24 hr and then concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-EtOAc (80:20) affords Int 1 as a white solid (68% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.0, 7.6, 7.4, 4.9, 4.8.

20 Step B. Preparation of ethyl *E*-4-(benzylamino)-2-butenate (Int 2).

Ethyl *E*-4-bromo-2-butenate (10 mL, 56 mmol, tech grade) is added to a stirred solution of benzylamine (16 mL, 146 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at rt. The reaction mixture stirs for 15 min, and is diluted with ether (1 L). The mixture is washed with saturated aqueous NaHCO<sub>3</sub> solution (3x) and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography

on silica gel. Elution with hexanes-EtOAc (70:30) affords Int 2 as a clear oil (62% yield):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.4-7.2, 7.0, 6.0, 4.2, 3.8, 3.4, 2.1-1.8, 1.3.

Step C. Preparation of *trans*-4-nitro-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (Int 3).

A solution of Int 1 (6.81 g, 34.9 mmol) and Int 2 (7.65 g, 34.9 mmol) in EtOH (70 mL) stirs at rt for 15 h and is then concentrated *in vacuo*. The residue is diluted with ether (100 mL) and saturated aqueous  $\text{NaHCO}_3$  solution (100 mL). The organic layer is separated and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-EtOAc (85:15) affords Int 3 as a clear oil (76% yield):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.4-7.3, 4.8-4.7, 4.1, 3.8-3.6, 3.3-3.0, 2.7-2.6, 2.4-2.3, 1.2.

Step D. Preparation of *trans*-4-amino-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (Int 4).

A mixture of Int 3 (3.28 g, 11.2 mmol) and  $\text{RaNi}$  (1.5 g) in EtOH (100 mL) is placed in a Parr bottle and hydrogenated for 4 h under an atmosphere of hydrogen (46 psi) at rt. The mixture is filtered through a pad of Celite, and the solvent is removed *in vacuo* to afford Int 4 as a clear oil (100% yield):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.3-7.2, 4.1, 3.6, 3.2, 3.0-2.9, 2.8, 2.8-2.6, 2.6-2.4, 2.30-2.2, 1.2.

Step E. Preparation of *trans*-4-(1,1-dimethylethoxycarbonylamido)-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (Int 5).

*Di-tert*-butyldicarbonate (3.67 g, 16.8 mmol) is added to a stirred solution of Int 4 (2.94 g, 11.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) cooled in an ice bath. The reaction is allowed to warm to rt and stirred overnight. The mixture is concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-EtOAc (80:20) affords Int 5 as a white solid (77% yield):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.4-7.2, 5.1-4.9, 4.1, 4.0-3.8, 3.6, 3.2-3.0, 2.8-2.6, 2.5-2.4, 2.3-2.1, 1.4, 1.3.

Step F. Preparation of *trans* (*tert*-butoxycarbonylamino)-4-(2-hydroxyethyl)-1-(*N*-phenylmethyl) pyrrolidine (Int 6).



LiAlH<sub>4</sub> powder (627 mg, 16.5 mmol) is added in small portions to a stirred solution of Int 5 (3.0 g, 8.3 mmol) in anhydrous THF (125 mL) in a -5°C bath. The mixture is stirred for 20 min in a -5°C bath, then quenched by the sequential addition of water (0.6 mL), 15% (w/v) aqueous NaOH (0.6 mL) and water (1.8 mL). Excess anhydrous K<sub>2</sub>CO<sub>3</sub> is added, and the mixture is stirred for 1 h, then filtered. The filtrate is concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel. Elution with EtOAc affords Int 6 as a white solid (94% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.4-7.3, 5.3-5.2, 4.1-4.0, 3.9-3.7, 3.3-3.2, 2.8-2.7, 2.3-2.1, 1.7, 1.5.

Int 6 is a racemic mixture that can be resolved via chromatography using a Diacel chiral pack AD column. From the two enantiomers thus obtained, the (+)-enantiomer, [α]<sub>D</sub><sup>25</sup> +35 (c 1.0, MeOH), gives rise to the corresponding optically pure *exo*-4-*S* final compounds, whereas the (-)-enantiomer, [α]<sub>D</sub><sup>25</sup> -34 (c 0.98, MeOH), gives rise to optically pure *exo*-4-*R* final compounds. The methods described herein use the (+)-enantiomer of Int 6 to obtain the optically pure *exo*-4-*S* final compounds. However, the methods used are equally applicable to the (-)-enantiomer of Int 6, making non-critical changes to the methods provided herein to obtain the optically pure *exo*-4-*R* final compounds.

Step G. Preparation of *exo* 3-(*tert*-butoxycarbonylamino)-1-azabicyclo[2.2.1]heptane (Int 7).

TEA (8.0 g, 78.9 mmol) is added to a stirred solution of Int 6 (2.5 g, 7.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), and the reaction is cooled in an ice-water bath. CH<sub>3</sub>SO<sub>2</sub>Cl (5.5 g, 47.8 mmol) is then added dropwise, and the mixture is stirred for 10 min in an ice-water bath. The resulting yellow mixture is diluted with saturated aqueous NaHCO<sub>3</sub> solution, extracted with CH<sub>2</sub>Cl<sub>2</sub> several times until no product remains in the aqueous layer by TLC. The organic layers are combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue is dissolved in EtOH (85 mL) and is heated to reflux for 16 h. The reaction mixture is allowed to cool to rt, transferred to a Parr bottle and treated with 10% Pd/C catalyst (1.25 g). The bottle is placed under an atmosphere of hydrogen (53 psi) for 16 h. The mixture is filtered through Celite, and fresh catalyst (10% Pd/C, 1.25 g) is added. Hydrogenolysis continues overnight. The process is repeated three more times until the

hydrogenolysis is complete. The final mixture is filtered through Celite and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel. Elution with  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$  (90:9.5:0.5) affords Int 7 as a white solid (46% yield):  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  5.6-5.5, 3.8-3.7, 3.3-3.2, 2.8-2.7, 2.0-1.8, 1.7-1.5, 1.5.

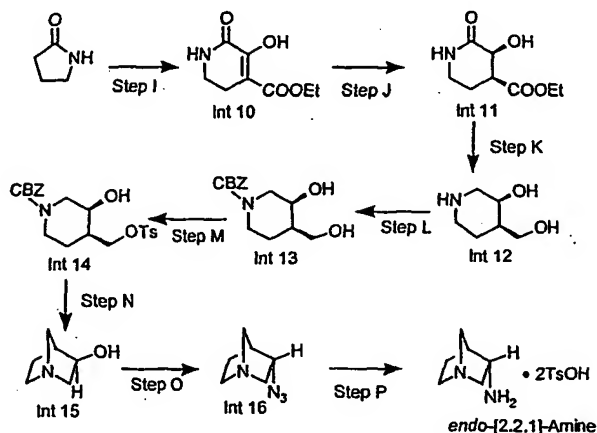
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Step H. Preparation of *exo*-3-amino-1-azabicyclo[2.2.1]heptane bis(hydro-*para*-toluenesulfonate).

*Para*-toluenesulfonic acid monohydrate (1.46 g, 7.68 mmol) is added to a stirred solution of Int 7 (770 mg, 3.63 mmol) in EtOH (50 mL). The reaction mixture is heated to reflux for 10 h, followed by cooling to rt. The precipitate is collected by vacuum filtration and washed with cold EtOH to give *exo*-[2.2.1]-Amine as a white solid (84% yield):  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  7.7, 7.3, 3.9-3.7, 3.7-3.3, 3.2, 2.4, 2.3-2.2, 1.9-1.8.

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Synthesis of *endo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro *para*-toluenesulfonate) salt (*endo*-[2.2.1]-Amine):



Step I. Preparation of ethyl 5-hydroxy-6-oxo-1,2,3,6-tetrahydropyridine-4-carboxylate (Int 10).

Absolute EtOH (92.0 mL, 1.58 mol) is added to a mechanically stirred suspension of potassium ethoxide (33.2 g, 395 mmol) in dry toluene (0.470 L). When the mixture is homogeneous, 2-pyrrolidinone (33.6 g, 395 mmol) is added, and then a solution of diethyl oxalate (53.1 mL, 390 mmol) in toluene (98 mL) is added via an addition funnel. After complete addition, toluene (118 mL) and EtOH (78 mL) are added sequentially. The mixture is heated to reflux for 18 h. The mixture is cooled to

rt and aqueous HCl (150 mL of a 6.0 M solution) is added. The mixture is mechanically stirred for 15 min. The aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers are dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to a yellow residue. The residue is recrystallized from EtOAc to afford Int 10 as a yellow solid (38% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 11.4, 7.4, 4.3, 3.4, 2.6, 1.3.

Step J. Preparation of ethyl *cis*-3-hydroxy-2-oxopiperidine-4-carboxylate (Int 11).

A mixture of Int 10 (15 g, 81 mmol) and 5% rhodium on carbon (2.0 g) in glacial acetic acid is placed under an atmosphere of hydrogen (52 psi). The mixture is shaken for 72 h. The mixture is filtered through Celite, and the filtrate is concentrated *in vacuo* to afford Int 11 as a white solid (98% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.3, 4.2, 4.0-3.8, 3.4, 3.3-3.2, 2.2, 1.3.

Step K. Preparation of *cis*-4-(hydroxymethyl)piperidin-3-ol (Int 12).

Int 11 (3.7 g, 19.9 mmol) as a solid is added in small portions to a stirred solution of LiAlH<sub>4</sub> in THF (80 mL of a 1.0 M solution) in an ice-water bath. The mixture is warmed to rt, and then the reaction is heated to reflux for 48 h. The mixture is cooled in an ice-water bath before water (3.0 mL, 170 mmol) is added dropwise, followed by the sequential addition of NaOH (3.0 mL of a 15% (w/v) solution) and water (9.0 mL, 500 mmol). Excess K<sub>2</sub>CO<sub>3</sub> is added, and the mixture is stirred vigorously for 15 min. The mixture is filtered, and the filtrate is concentrated *in vacuo* to afford Int 12 as a yellow powder (70% yield): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 4.3, 4.1, 3.7, 3.5-3.2, 2.9-2.7, 2.5-2.3, 1.5, 1.3.

25

Step L. Preparation of benzyl *cis*-3-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate (Int 13).

*N*-(benzyloxy carbonyloxy)succinimide (3.04 g, 12.2 mmol) is added to a stirred solution of Int 12 (1.6 g, 12.2 mmol) in saturated aqueous NaHCO<sub>3</sub> (15 mL) at rt. The mixture is stirred at rt for 18 h. The organic and aqueous layers are separated. The aqueous layer is extracted with ether (3X). The combined organic layers are dried over anhydrous K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated *in vacuo* to afford Int 13 as a yellow

oil (99% yield):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.4-7.3, 5.2, 4.3, 4.1, 3.8-3.7, 3.0-2.8, 2.1, 1.9-1.7, 1.4.

Step M. Preparation of benzyl *cis*-3-hydroxy-4-[(4-methylphenyl)sulfonyl oxymethyl]piperidine-1-carboxylate (Int 14).

*Para*-toluenesulfonyl chloride (1.0 g, 5.3 mmol) is added to a stirred solution of Int 13 (3.6 g, 5.3 mmol) in pyridine (10 mL) in a  $-15^\circ\text{C}$  bath. The mixture is stirred for 4 h, followed by addition of HCl (4.5 mL of a 6.0 M solution).  $\text{CH}_2\text{Cl}_2$  (5 mL) is added. The organic and aqueous layers are separated. The aqueous layer is extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers are washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford Int 14 as a colorless oil (78% yield):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.8, 7.4-7.2, 5.1, 4.3-4.2, 4.1, 3.9-3.8, 2.9-2.7, 2.4, 1.9, 1.6-1.3.

Step N. Preparation of *exo*-1-azabicyclo[2.2.1]heptan-3-ol (Int 15).

A mixture of Int 14 (3.6 g, 8.6 mmol) and 10% Pd/C catalyst (500 mg) in EtOH (50 mL) is placed under an atmosphere of hydrogen. The mixture is shaken for 16 h. The mixture is filtered through Celite. Solid  $\text{NaHCO}_3$  (1.1 g, 13 mmol) is added to the filtrate, and the mixture is heated in an oil bath at  $50^\circ\text{C}$  for 5 h. The solvent is removed *in vacuo*. The residue is dissolved in saturated aqueous  $\text{K}_2\text{CO}_3$  solution. Continuous extraction of the aqueous layer using a liquid-liquid extraction apparatus (18 h), followed by drying the organic layer over anhydrous  $\text{K}_2\text{CO}_3$  and removal of the solvent *in vacuo* affords Int 15 as a white solid (91% yield):  $^1\text{H}$  NMR  $\delta$  3.8, 3.0-2.8, 2.6-2.5, 2.4-2.3, 1.7, 1.1.

Step O. Preparation of *endo*-3-azido-1-azabicyclo[2.2.1]heptane (Int 16).

To a mixture of Int 15 (1.0 g, 8.9 mmol) and triphenyl phosphine (3.0 g, 11.5 mmol) in toluene-THF (50 mL, 3:2) in an ice-water bath are added sequentially a solution of hydrazoic acid in toluene (15 mL of ca. 2 M solution) and a solution of diethyl azadicarboxylate (1.8 mL, 11.5 mmol) in toluene (20 mL). The mixture is allowed to warm to rt and stir for 18 h. The mixture is extracted with aqueous 1.0M HCl solution. The aqueous layer is extracted with EtOAc, and the combined organic layers are discarded. The pH of the aqueous layer is adjusted to 9 with 50% aqueous NaOH solution. The aqueous layer is extracted with  $\text{CH}_2\text{Cl}_2$  (3X), and the combined

organic layers are washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH (92:7:1) affords Int 16 as a colorless oil (41% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.1, 3.2, 2.8, 2.7-2.5, 2.2, 1.9, 1.5.

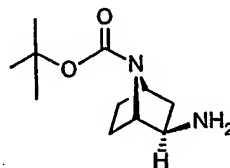
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Step P. Preparation of *endo*-3-amino-1-azabicyclo[2.2.1]heptane bis(hydro-*para*-toluenesulfonate).

A mixture of Int 16 (250 mg, 1.8 mmol) and 10% Pd/C catalyst (12 mg) in EtOH (10 mL) is placed under an atmosphere of hydrogen (15 psi). The mixture is stirred for 1 h at rt. The mixture is filtered through Celite, and the filtrate is concentrated *in vacuo*. The residue is dissolved in EtOH (10 mL) and *para*-toluenesulfonic acid monohydrate (690 mg, 3.7 mmol) is added. The mixture is stirred for 30 min, and the precipitate is filtered. The precipitate is washed sequentially with cold EtOH and ether. The precipitate is dried *in vacuo* to afford *endo*-[2.2.1]-Amine as a white solid (85% yield): <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.7, 7.3, 4.2, 3.9, 3.6-3.4, 3.3-3.2, 2.4, 2.3, 2.1.

15

Preparation of *exo-tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate (7-aza-[2.2.1]-Amine):



7-aza-[2.2.1]-Amine

20

Preparation of methyl-3-bromo-propiolate:

Methyl propiolate (52 ml, 0.583 mole) is combined with recrystallized *N*-bromo-succinimide (120 g, 0.674 mole) in 1,700 ml acetone under nitrogen. The solution is treated with silver nitrate (9.9 g, 0.0583 mole) neat in a single lot and the reaction is stirred 6 h at RT. The acetone is removed under reduced pressure (25°C, bath temperature) to provide a gray slurry. The slurry is washed with 2 x 200 ml hexane, the gray solid is removed by filtration, and the filtrate is concentrated *in vacuo* to provide 95 g of a pale yellow oily residue. The crude material was distilled via short path under reduced pressure (65°C, about 25 mm Hg) into a dry ice/acetone

25

cooled receiver to give 83.7 g (88%) of methyl-3-bromo-propiolate as a pale yellow oil. Anal. calc'd for  $C_4H_3BrO_2$ : C, 29.48; H, 1.86. Found: C, 29.09; H, 1.97.

Preparation of 7-*tert*-butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-  
5 diene-2,7-dicarboxylate.

Methyl-3-bromo-propiolate (83.7 g, 0.513 mole) is added to *N*-*t*-butoxy-pyrrole (430 ml, 2.57 mole) under nitrogen. The dark mixture is warmed in a 90 °C bath for 30 h, is cooled, and the bulk of the excess *N*-*t*-butoxy-pyrrole is removed *in vacuo* using a dry ice/acetone condenser. The dark oily residue is chromatographed  
10 over 1 kg silica gel (230-400 mesh) eluting with 0-15% EtOAc/hexane. The appropriate fractions are combined and concentrated to afford 97 g (57%) of 7-*tert*-butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate as a dark yellow oil. HRMS (FAB) calc'd for  $C_{13}H_{16}BrNO_4 + H$ : 330.0341, found 330.0335 ( $M+H$ )<sup>+</sup>.

15

Preparation of (+/-) *Endo*-7-*tert*-butyl 2-methyl 7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate.

7-*tert*-Butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate (97 g, 0.294 mole) is added to 10% Pd/C (6.8g) in 900 ml absolute  
20 EtOH in a PARR bottle. The suspension is diluted with a solution of  $NaHCO_3$  (25 g, 0.301 mole) in 250 ml water and the mixture is hydrogenated at 50 PSI for 2.5 h. The catalyst is removed by filtration, is washed with fresh EtOH, and the filtrate is concentrated *in vacuo* to give a residue. The residue is partitioned between 1 x 200 ml saturated  $NaHCO_3$  and  $CH_2Cl_2$  (4 x 100 ml). The combined organic layer is dried  
25 over 1:1 anhydrous  $K_2CO_3$ /anhydrous  $MgSO_4$  and concentrated *in vacuo* to afford 72.8 g (98%) of (+/-) *endo*-7-*tert*-butyl 2-methyl 7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate. MS (EI) for  $C_{14}H_{22}O_4$ ,  $m/z$ : 255 ( $M$ )<sup>+</sup>.

Preparation of (+/-) *exo*-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-  
30 2-carboxylic acid.

(+/-)*Endo*-7-*tert*-butyl 2-methyl 7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate (72.8 g, 0.285 mole) is dissolved in 1000 ml dry MeOH in a dried flask under nitrogen. The solution is treated with solid NaOMe (38.5 g, 0.713 mole) neat, in a

single lot and the reaction is warmed to reflux for 4h. The mixture is cooled to 0°C, is treated with 400 ml water, and the reaction is stirred 1h as it warms to RT. The mixture is concentrated *in vacuo* to about 400 ml and the pH of the aqueous residue is adjusted to 4.5 with 12N HCl. The precipitate is collected and dried. The tan, slightly tacky solid is washed with 2 x 100 ml 60% ether in hexane and is dried to provide 47 g (68%) of *exo*-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid as an off-white powder. HRMS (FAB) calc'd for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>+H: 242.1392, found 242.1390 (M+H)<sup>+</sup>.

10 Preparation of (+/-) *exo-tert*-butyl 2-[[*(benzyloxy)*carbonyl]amino]-7-azabicyclo[2.2.1]heptane-7-carboxylate.

(+/-)*Exo*-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (32.5 g, 0.135 mole) is combined with TEA (24.4 ml, 0.175 mole) in 560 ml dry toluene in a dry flask under nitrogen. The solution is treated drop-wise with diphenylphosphoryl azide (37.7 ml, 0.175 mole), and is allowed to stir for 20 min at RT. The mixture is treated with benzyl alcohol (18.1 ml, 0.175 mole), and the reaction is stirred overnight at 50°C. The mixture is cooled, is extracted successively with 2 x 250 ml 5% citric acid, 2 x 200 ml water, 2 x 200 ml saturated sodium bicarbonate, and 2 x 100 ml saturated NaCl. The organic layer is dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to an amber oil. The crude material was chromatographed over 800 g silica gel (230-400 mesh), eluting with 15-50% EtOAc/hexane. The appropriate fractions are combined and concentrated to give 44 g (94%) of (+/-) *exo-tert*-butyl 2-[[*(benzyloxy)*carbonyl]amino]-7-azabicyclo[2.2.1]heptane-7-carboxylate as a pale oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.29-1.60, 1.44, 1.62-2.01, 3.76-3.88, 4.10, 4.24, 5.10, 7.36 ppm.

Preparation of *exo-tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-2-[[*(benzyloxy)*carbonyl]amino]-7-azabicyclo[2.2.1]heptane-7-carboxylate and *exo-tert*-butyl (1*R*, 2*S*, 4*S*)-(-)-2-[[*(benzyloxy)*carbonyl]amino]-7-azabicyclo[2.2.1]heptane-7-carboxylate.

30 The isolated (+/-) *exo-tert*-butyl 2-[[*(benzyloxy)*carbonyl]amino]-7-azabicyclo[2.2.1]heptane-7-carboxylate is resolved via preparative chiral HPLC (50x500 mm Chiralcel OJ column, 30 deg. C, 70 mL/min. 10/90 (v/v) isopropanol/heptane). The resolution affords 10.5 g of *exo-tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-

2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate and 15.5 g of *exo-tert*-butyl-(1*R*, 2*S*, 4*S*)-(-)-2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate.

The 2*R* enantiomer is triturated with 12 ml ether followed by 12 ml hexane (to remove lingering diastereo and enantiomeric impurities) and is dried to afford 9.5 g (43%) of purified *exo-tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate with 99% enantiomeric excess. MS (EI) for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>, *m/z*: 346 (M)<sup>+</sup>. [α]<sub>D</sub><sup>25</sup> = 22, (c 0.42, chloroform).

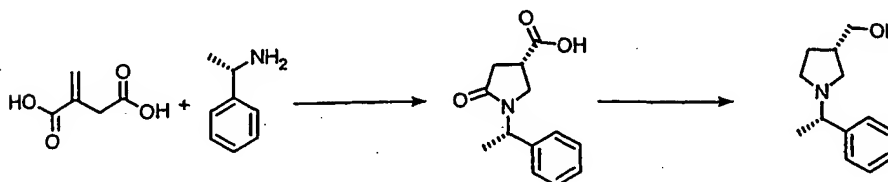
The 2*S* enantiomer is triturated with 20 ml ether followed by 20 ml hexane to give 14 g (64%) of purified *exo-tert*-butyl (1*R*, 2*S*, 4*S*)-(-)-2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate with 99% enantiomeric excess. MS (EI) for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>, *m/z*: 346 (M)<sup>+</sup>. [α]<sub>D</sub><sup>25</sup> = -23, (c 0.39, chloroform).

Preparation of *exo-tert*-butyl-(1*S*, 2*R*, 4*R*)-(+)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate (7-aza-[2.2.1]-Amine).

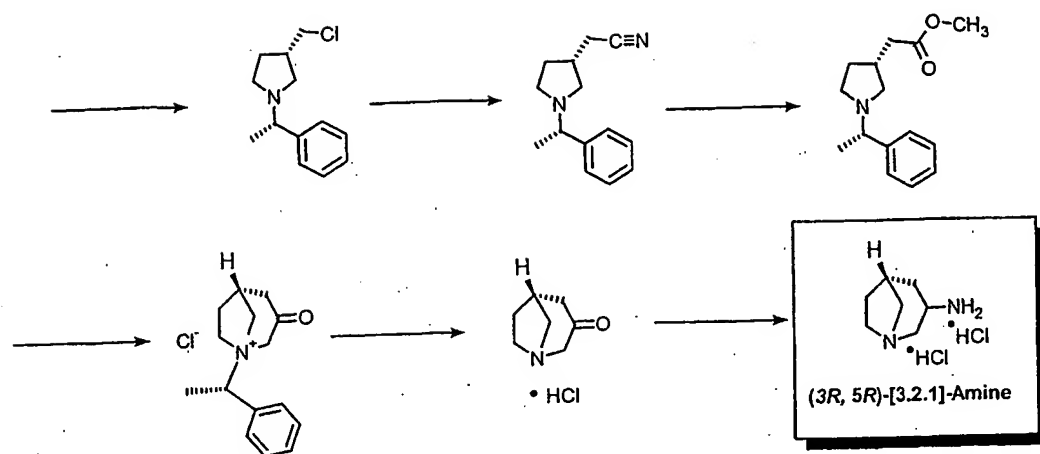
*Exo-tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate (9.5 g, 27.4 mmol) is combined with 950 mg 10% Pd/C in 75 ml absolute EtOH in a 500 ml Parr bottle. The reaction mixture is hydrogenated at 50 PSI for 3h, the catalyst is removed by filtration, and the filter cake was washed with MeOH. The filtrate is concentrated *in vacuo* to give 6.4 g of a residue. The crude material is chromatographed over 200 g silica gel (230-400 mesh) eluting with 7% CH<sub>3</sub>OH/CHCl<sub>3</sub> containing 1% conc. NH<sub>4</sub>OH. The appropriate fractions are combined and concentrated to give 5.61 g (96%) of *exo-tert*-butyl-(1*S*, 2*R*, 4*R*)-(+)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate as a pale oil. MS (EI) for C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>, *m/z*: 212 (M)<sup>+</sup>. [α]<sub>D</sub><sup>25</sup> = 9, (c 0.67, chloroform).

#### Preparation of 1-azabicyclo[3.2.1]octan-3-amine:

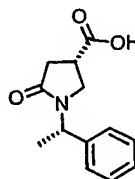
#### Preparation of the 3*R*,5*R*-[3.2.1]-Amine:







**(3S)-1-[(S)-1-Phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid:**

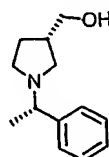


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According to the literature procedure (Nielsen *et al.* J. Med. Chem 1990, 70-77), a mixture of itaconic acid (123.17 g, 946.7 mmol) and (S)-(-)- $\alpha$ -methyl benzylamine (122.0 mL, 946.4 mmol) were heated (neat) in a 160°C oil bath for 4 h. Upon cooling, MeOH (~200 mL) was added and the resulting solid collected by filtration. The solid was treated with EtOH (~700 mL) and warmed using a steam bath until ~450 mL solvent remained. After cooling to rt, the solid was collected and dried to afford 83.2 g as a white crystalline solid:  $[\alpha]^{25}_D = -80$  (*c* 0.97, DMSO). MS (EI)  $m/z$  233 ( $M^+$ ).

The lack of a resonance 3.59 indicates a single diastereomer. The other diastereomer can be retrieved from the initial MeOH tritulant. Attempts to crystallize this material generally led to small quantities of (3R)-1-[(S)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid.

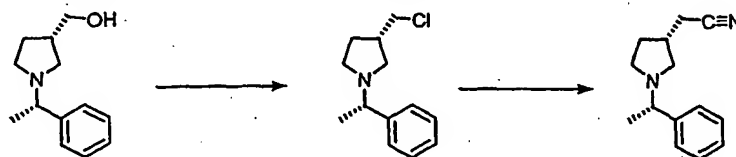
**(3S)-1-[(S)-1-Phenethyl]-3-(hydroxymethyl)pyrrolidine:**



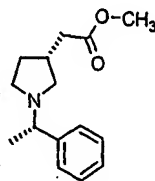
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A suspension (3*S*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid (82.30 g, 352.8 mmol) in Et<sub>2</sub>O (200 mL) was added in small portions to a slurry of LiAlH<sub>4</sub> (17.41 g, 458.6 mmol) in Et<sub>2</sub>O (700 mL). The mixture began to reflux during the addition. The addition funnel containing the suspension was rinsed with Et<sub>2</sub>O (2 x 50 mL), and the mixture was heated in a 50 °C oil bath for an additional 2 h and first allowed to cool to rt and then further cooled using an ice bath. The mixture was carefully treated with H<sub>2</sub>O (62 mL). The resulting precipitate was filtered, rinsed with Et<sub>2</sub>O, and discarded. The filtrate was concentrated to a yellow oil. When EtOAc was added to the oil, a solid began to form. Hexane was then added and removed by filtration and dried to afford 43.3 g as a white solid.  $[\alpha]_D^{25} = -71$  (*c* 0.94, CHCl<sub>3</sub>). MS (EI) *m/z* 205 (*M*<sup>+</sup>).

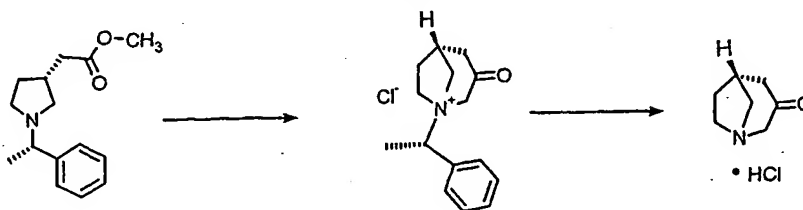
**(3*R*)-1-[(*S*)-1-Phenethyl]-3-(cyanomethyl)pyrrolidine:**



A solution of (3*S*)-1-[(*S*)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine (42.75 g, 208.23 mmol) in chloroform (350 mL) was heated to reflux under N<sub>2</sub>. The solution was treated with a solution of thionyl chloride (41.8 mL, 573 mmol) in chloroform (40 mL) dropwise over 45 min. The mixture stirred for an additional 30 min, was cooled and concentrated. The residue was diluted with H<sub>2</sub>O (~200 mL), 1 N NaOH was added until a pH ~ 8 (pH paper). A small portion (~50 mL) of sat. NaHCO<sub>3</sub> was added and the basic mixture was extracted with EtOAc (3 x 400 mL), washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give 46.51 g of a red-orange oil for (3*S*)-1-[(*S*)-1-phenethyl]-3-(chloromethyl)pyrrolidine: *R<sub>f</sub>*: 0.50 (EtOAc-hexane 1:1); MS (ESI<sup>+</sup>) *m/z* 224.2 (*M*H<sup>+</sup>). The chloride (46.35 g, 208.0 mmol) was transferred to a flask, dimethyl sulfoxide (200 mL) was added, and the solution was treated with NaCN (17.84 g, 363.9 mmol). The mixture was heated under N<sub>2</sub> in a 100°C oil bath overnight and was cooled. The brown mixture was poured into H<sub>2</sub>O (300 mL) and extracted with EtOAc (1000 mL in portions). The combined organic layer was washed with H<sub>2</sub>O (6 x ~50 mL), brine (~100 mL), dried (MgSO<sub>4</sub>), filtered and concentrated to give 40.61 g as an orange-red oil: *R<sub>f</sub>*: 0.40 (EtOAc-PhCH<sub>3</sub> 1:1). MS (ESI<sup>+</sup>) for *m/z* 215.2 (*M*+H<sup>+</sup>).

**(3R)-Methyl 1-[(S)-1-phenylethyl]pyrrolidine-3-acetate:**

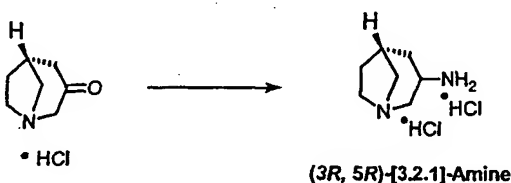
Acetyl chloride (270 mL, 3.8 mol) was carefully added to a flask containing  
 5 chilled (0°C) methanol (1100 mL). After the addition was complete, the acidic  
 solution stirred for 45 min (0 °C) and then (3R)-1-[(S)-1-phenethyl]-3-  
 (cyanomethyl)pyrrolidine (40.50 g, 189.0 mmol) in methanol (200 mL) was added.  
 The ice bath was removed and the mixture stirred for 100 h at rt. The resulting  
 suspension was concentrated. Water (~600 mL) was added, the mixture stirred for 45  
 10 min and then the pH was adjusted (made basic) through the addition of ~700 mL sat.  
 aq. NaHCO<sub>3</sub>. The mixture was extracted with EtOAc (3 x 300 mL). The combined  
 organics were washed with brine, dried (MgSO<sub>4</sub>), filtered through celite and  
 concentrated to give 36.86 g as an orange-red oil. MS (ESI+) *m/z* 248.2 (M+H<sup>+</sup>).

**(5R)-1-Azabicyclo[3.2.1]octan-3-one hydrochloride:**

A solution of (3R)-methyl 1-[(S)-1-phenylethyl]pyrrolidine-3-acetate (25.72g,  
 104.0 mmol) in THF (265 mL) was cooled under N<sub>2</sub> in a CO<sub>2</sub>/acetone bath. Next,  
 ICH<sub>2</sub>Cl (22.7 mL, 312.0 mmol) was added, and the mixture stirred for 30 min. A  
 20 solution of 2.0M lithium diisopropylamide (heptane/THF/ethylbenzene, 156 mL, 312  
 mmol) was added slowly over 30 min. The internal temperature reached a maximum  
 of -40°C during this addition. After 1 h, sat. NH<sub>4</sub>Cl (100 mL) was added and the  
 mixture was allowed to warm to rt. The organic layer was separated, dried (MgSO<sub>4</sub>),  
 filtered and concentrated. The resulting red-brown foam was chromatographed (300 g  
 25 SiO<sub>2</sub>, CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH (89:10:1) followed by CHCl<sub>3</sub>-MeOH (3:1). The product  
 fractions were pooled and concentrated to afford (5R)-3-oxo-1-[(1S)-1-phenylethyl]-1-  
 azoniabicyclo[3.2.1]octane chloride (10.12g) as a tan foam (MS (ESI+) *m/z* 230.1

(M+H<sup>+</sup>). This foam (10.1 g, 38 mmol) was taken up in MeOH (500 mL), 10% Pd(C) (3.0 g) added and the mixture was hydrogenated (45 psi) overnight. The mixture was filtered and re-subjected to the reduction conditions (9.1 g, 10% Pd/C, 50 psi). After 5 h, TLC indicated the consumption of the (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azabicyclo[3.2.1]octane chloride. The mixture was filtered, concentrated and trituated (minimal *i*PrOH) to give 3.73 g in two crops, as an off-white solid:  $[\alpha]_D^{25} = 33$  (*c* 0.97, DMSO). MS (EI) *m/z* 125 (M<sup>+</sup>).

**(3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine dihydrochloride:**

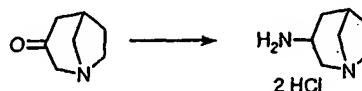


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To a flask containing (5*R*)-1-azabicyclo[3.2.1]octan-3-one hydrochloride (3.64 g, 22.6 mmol), hydroxylamine hydrochloride (2.04 g, 29.4 mmol), and ethanol (130 mL) was added sodium acetate trihydrate (9.23 g, 67.8 mmol). The mixture stirred for 3 h and was filtered and concentrated. The resulting white solid was taken up in *n*-propanol (100 mL) and sodium (~13.6 g, 618 mmol) was added over 20-25 portions. The reaction spontaneously began to reflux, and the reaction was heated in an oil bath (100°C). The addition was complete in ~20 min and the mixture had solidified after ~40 min. The oil bath was removed and *n*-propanol (2 x 25 mL) was added dissolving the remaining sodium metal. The mixture was carefully quenched through the dropwise addition of H<sub>2</sub>O (100 mL). Saturated aq. NaCl (20 mL) was added, and the layers were separated. The organic layer was dried (MgSO<sub>4</sub>), filtered, treated with freshly prepared MeOH/HCl, and concentrated. The resulting solid was trituated with 30 mL EtOH, filtered and dried *in vacuo* to afford 3.51 g as a white solid:  $[\alpha]_D^{25} = -3$  (*c* 0.94, DMSO). MS (FAB) *m/z* 127 (MH<sup>+</sup>).

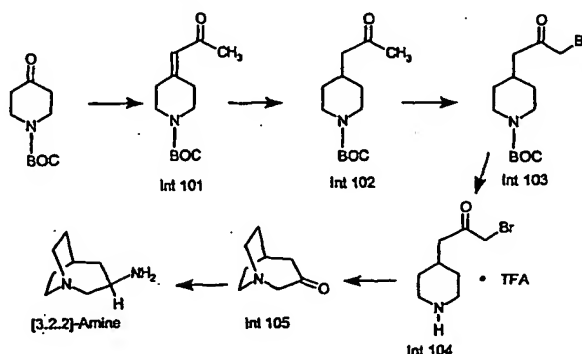
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**Preparation of *endo*-1-azabicyclo[3.2.1]octan-3-amine dihydrochloride (*endo*-[3.2.1]-Amine):**



A mixture of 1-azabicyclo[3.2.1]octan-3-one hydrochloride (2.80 g, 17.3 mmol), ethanol (25 mL), and hydroxylamine hydrochloride (1.56 g, 22.4 mmol) is treated with sodium acetate trihydrate (7.07 g, 51.2 mmol). The mixture is stirred for 3 h and evaporated *in vacuo*. The residue is diluted with CH<sub>2</sub>Cl<sub>2</sub>, treated with charcoal, filtered and evaporated. The resulting oxime (3.1 mmol) is treated with acetic acid (30 mL) and hydrogenated at 50 psi over PtO<sub>2</sub> (50 mg) for 12 h. The mixture is then filtered and evaporated. The residue is taken up in a minimal amount of water (6 mL) and the pH is adjusted to >12 using solid NaOH. The mixture is then extracted with ethyl acetate (4 X 25 mL), dried over MgSO<sub>4</sub>, filtered, treated with ethereal HCl, and evaporated to give the give *endo*-[3.2.1]-Amine.

### Preparation of the 3.2.2 Amines:



### *tert*-Butyl 4-(2-oxopropylidene)piperidine-1-carboxylate (Int 101):

Sodium hydride (60% oil dispersion, 2.01 g, 50.2 mmol) is washed with pentane (3X) and suspended in dry THF (40 mL). The solution is cooled to 0°C before diethyl (2-oxopropyl)phosphonate (9.75 g, 50.2 mmol) is added dropwise. After complete addition, the solution is warmed to rt and stirred for 30 min. *tert*-Butyl 4-oxo-1-piperidinecarboxylate (5.0g, 25.1 mmol) is added in portions over 10 min, followed by stirring at rt for 2 h. A saturated aqueous solution of ammonium chloride is added, followed by dilution with ether. The organic layer is extracted with water. The organic layer is dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated to a yellow oil. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-ether (60:40) gave 4.5 g (75%) of Int 101 as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.2, 3.5, 3.4, 2.9, 2.3, 2.2, 1.5.

### Preparation of *tert*-butyl 4-(2-oxopropyl)piperidine-1-carboxylate (Int 102):

A mixture of Int 101 (4.5 g, 19 mmol) and 10% palladium on activated carbon (450mg) in EtOH (150 mL) is placed in a Parr bottle and hydrogenated for 5 h at 50 psi. The mixture is filtered through Celite, and the filtrate is concentrated *in vacuo* to afford 4.3 g (94%) of Int 102 as a clear oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.1, 2.8, 2.4, 2.2, 2.0, 1.7, 1.5, 1.1.

*tert*-Butyl 4-(3-bromo-2-oxopropyl)piperidine-1-carboxylate (Int 103):

To a stirred solution lithium hexamethyldisilylamide in THF (20.0 mL, 1.0 M) in a  $-78^\circ\text{C}$  bath is added chlorotrimethylsilane (11.0 mL, 86.4 mmol) dropwise. The mixture is stirred at  $-78^\circ\text{C}$  for 20 min, followed by addition of Int 102 (3.21 g, 13.3 mmol) in a solution of THF (50 mL) dropwise. After complete addition, the mixture is stirred at  $-78^\circ\text{C}$  for 30 min. The mixture is warmed to  $0^\circ\text{C}$  in an ice-water bath and phenyltrimethylammonium tribromide (5.25 g, 14.0 mmol) is added. The mixture is stirred in an ice-bath for 30 min, followed by the addition of water and ether. The aqueous layer is washed with ether, and the combined organic layers are washed with saturated aqueous sodium thiosulfate solution. The organic layer is dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford a yellow oil. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-ether (60:40) gave 2.2 g (52%) of Int 103 as a lt. yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.2-4.1, 3.9, 2.8, 2.7, 2.6, 2.1-2.0, 1.7, 1.5, 1.2-1.1.2.

1-Bromo-3-piperidin-4-ylacetone trifluoroacetate (Int 104):

To a stirred solution of Int 103 (2.2 g, 6.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) in an ice-water bath is added trifluoroacetic acid (10 mL, 130 mmol). The mixture is stirred at  $0^\circ\text{C}$  for 30 min. The volatiles are removed *in vacuo* to afford 2.0 g (87%) of Int 104 as a yellow residue: MS (ESI) for  $\text{C}_8\text{H}_{15}\text{BrNO}$   $[\text{M}+\text{H}]^+ m/e$  220.

1-Azabicyclo[3.2.2]nonan-3-one (Int 105):

To a stirred solution of DIEA (13 mL) in acetonitrile (680 mL) at reflux temperature is added a solution of Int 104 (2.0 g, 6.0 mmol) in acetonitrile (125 mL) over a 4 h period via syringe pump. The mixture is kept at reflux temperature overnight. The mixture is concentrated *in vacuo* and the remaining residue is partitioned between a saturated aqueous potassium carbonate solution and  $\text{CHCl}_3$ -

MeOH (90:10). The aqueous layer is extracted with  $\text{CHCl}_3$ -MeOH (90:10), and the combined organic layers are dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to a brown oil. The crude product is purified by flash chromatography on silica gel. Elution with  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$  (95:4.5:0.5) gives 600 mg (72%) of Int 105 as a clear solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.7, 3.3-3.2, 3.1-3.0, 2.7, 2.3, 2.0-1.8.

1-Azabicyclo[3.2.2]nonan-3-amine bis(4-methylbenzenesulfonate) ([3.2.2]-Amine):

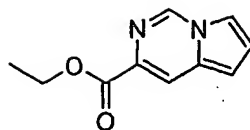
To a stirred mixture of Int 105 (330 mg, 2.4 mmol) and sodium acetate·trihydrate (670 mg, 4.8 mmol) in EtOH (6.0 mL) is added hydroxylamine·hydrochloride (200 mg, 2.8 mmol). The mixture is stirred at rt for 10 h. The mixture is filtered and the filtrate is concentrated *in vacuo* to a yellow solid. To a solution of the solid (350 mg, 2.3 mmol) in *n*-propanol (30 mL) at reflux temperature is added sodium metal (2.0 g, 87 mmol) in small portions over 30 min. Heating at reflux is continued for 2 h. The solution is cooled to rt and brine is added. The mixture is extracted with *n*-propanol, and the combined organic layers are concentrated *in vacuo*. The residue is taken up in  $\text{CHCl}_3$  and the remaining solids are filtered. The filtrate is dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to a clear solid. To a stirred solution of the solid (320 mg, 2.3 mmol) in EtOH (4 mL) is added *p*-toluenesulfonic acid monohydrate (875 mg, 4.6 mmol). The solution is warmed in a water bath to 45°C for 30 min, followed by concentration of the solvent to afford 710 mg (62%) of [3.2.2]-Amine as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.7, 7.3, 4.1-3.9, 3.6-3.4, 2.6-2.5, 2.4, 2.2-2.1, 2.1-2.0, 1.9.

Resolution of stereoisomers:

The amine can be coupled to form the appropriate amides or thioamides as a racemic mixture. The racemic mixture can then be resolved by chromatography using chiral columns or chiral HPLC, techniques widely known in the art, to provide the requisite resolved enantiomers 3(*R*) and 3(*S*) of said amides.

## ACIDS

Ethyl pyrrolo[1,2-*c*]pyrimidine-3-carboxylate:



A solution of pyrrole-2-carboxaldehyde (3.6g, 38.1mmol) in 40mL dry THF is added to ethyl isocyanoacetate (4.3g, 38.1mmol) and DBU (5.8g, 38.2mmol) in 60mL dry THF. After stirring at RT overnight, the reaction is neutralized with 10% AcOH.

- 5 The solvent is removed *in vacuo*. The residue is taken up in EtOAc/H<sub>2</sub>O, the aqueous layer is extracted with EtOAc, dried (MgSO<sub>4</sub>), filtered and concentrated. The residue is purified by flash chromatography on silica gel eluting with 30-70% EtOAc/hexanes. The carboxylate is obtained (4.45g, 61%) as an off-white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.86, 8.24, 7.54, 7.01, 6.78, 4.45, 1.44.

10

The following compounds are made from the corresponding pyrrole-2-carboxaldehydes, making non-critical variations:

- Ethyl 7-chloropyrrolo[1,2-c]pyrimidine-3-carboxylate. Yield 25% starting from 5-chloropyrrole-2-carboxaldehyde. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.86, 8.21, 6.91-6.89, 6.80-6.77, 4.50-4.43, 1.47-1.42.

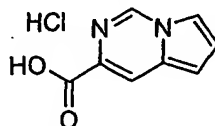
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Ethyl 6-chloropyrrolo[1,2-c]pyrimidine-3-carboxylate. Yield 49% starting from 4-chloropyrrole-2-carboxaldehyde. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.76, 8.14, 7.51, 6.72, 4.49-4.42, 1.46-1.41.

- Ethyl 6-bromopyrrolo[1,2-c]pyrimidine-3-carboxylate. Yield 9% starting from 4-bromopyrrole-2-carboxaldehyde. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.77, 8.15, 7.55, 6.79, 4.49-4.42, 1.46-1.41.

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Pyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride:



- 25 Ethyl pyrrolo[1,2-c]pyrimidine-3-carboxylate (4.1g, 21.2mmol) is dissolved/suspended in 100mL concentrated HCl. The mixture is heated under reflux. After 4h, the reaction is cooled and the solvent is removed *in vacuo*. Absolute EtOH is added and the solvent is removed (twice) to afford a yellow-green solid. The solid is triturated with Et<sub>2</sub>O and dried to give 4.28g (100%) of pyrrolo[1,2-c]pyrimidine-3-



carboxylic acid as the hydrochloride salt. The solid can be recrystallized from EtOH.

$^1\text{H}$  NMR (400MHz, DMSO)  $\delta$  9.24, 8.21, 7.90, 7.06, 6.85.

The following compounds are made from the corresponding ethyl pyrrolo[1,2-

5 c]pyrimidine-3-carboxylates, making non-critical variations:

7-Chloropyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride. Yield 77%.  $^1\text{H}$

NMR (400MHz,  $d_6$ -DMSO)  $\delta$  9.3, 9.04, 8.25, 7.16-7.14, 6.96-6.94.

6-Chloropyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride. Yield 95%.  $^1\text{H}$

NMR (400MHz,  $d_6$ -DMSO)  $\delta$  11.15, 9.14, 8.15, 8.04, 6.91.

10 6-Bromopyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride. Yield 97%.  $^1\text{H}$

NMR (400MHz,  $d_6$ -DMSO)  $\delta$  10.2, 9.12, 8.15, 8.04, 6.96.

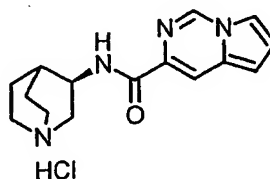
### COUPLINGS

The following examples are provided as examples and are not intended to

15 limit the scope of this invention to only those provided examples and named compounds. Also, the salts made in the examples are only exemplary and are not intended to limit the invention. Any pharmaceutically acceptable salt can be made by one of ordinary skill in the art. Further, the naming of specific stereoisomers is for exemplification, and is not intended to limit in anyway the scope of the invention.

20 The invention includes the following examples in pure stereoisomeric form or as racemic mixtures. Any of the amines discussed herein can be coupled with the acids discussed herein using the methods discussed herein, making non-critical changes, to obtain other compounds within the scope of the present invention.

25 **Example 1:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-c]pyrimidine-3-carboxamide hydrochloride:

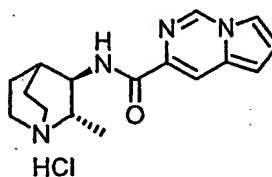


Pyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride (0.33g, 1.66mmol) and TEA (2.0mL, 14.35mmol) are dissolved in 15mL THF. Diphenylphosphinic chloride (0.47g, 1.99mmol) is added dropwise. After 1h, (R)-(+)-3-aminoquinuclidine

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dihydrochloride is added and the reaction is allowed to stir at RT. After 1 day, 1N NaOH is added and the mixture is extracted with  $\text{CHCl}_3$ . The combined organic layers are dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue is purified by chromatography (Biotage 40S, 90:9:1  $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ ) to afford 0.45g (100%) of product. The hydrochloride salt is prepared and recrystallized from  $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$ . HRMS (FAB) calcd for  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}+\text{H}$  271.1555, found 271.1559.

**Example 2:** *N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide hydrochloride:

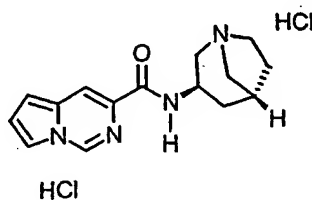


Pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride (0.16g, 0.82mmol), HATU (0.47g, 1.22mmol) and 2-methyl-2.2.2-Amine (0.21g, 1.0mmol) are suspended in 15mL  $\text{CH}_3\text{CN}$ . DIEA (1.4mL, 8.0mmol) is added dropwise. After 2 days, the solvent is removed and the residue is taken up in 1N NaOH and  $\text{CHCl}_3$ . The aqueous layer is extracted with  $\text{CHCl}_3$ , dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue is purified by chromatography (Biotage 40S, 90:9:1  $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ ), and the hydrochloride salt is prepared and recrystallized from  $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$  to provide 0.059g (23%) of the product. HRMS (FAB) calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}+\text{H}$  285.1715, found 285.1717.

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**Example 3:** *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide dihydrochloride:



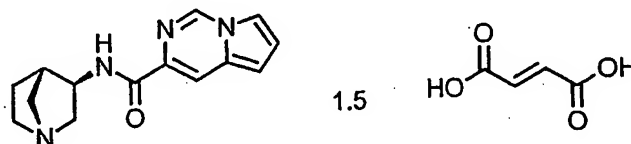
A mixture of *exo*-3*R*,5*R*-[3.2.1]-Amine (0.221 g, 1.11 mmol), pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride (0.220 g, 1.11 mmol), THF (18 mL), DIEA (0.77 mL, 4.4 mmol), and DMF (4 mL) is cooled in an ice bath and treated with HATU (0.426 g, 1.12 mmol). The mixture is allowed to warm to RT overnight and is

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evaporated. The residue is purified by flash column chromatography (1:9:90; conc.  $\text{NH}_4\text{OH}-\text{MeOH}-\text{CHCl}_3$ ). The dihydrochloride salt is formed and triturated with  $\text{EtOH}/\text{Et}_2\text{O}$  to yield the desired product (0.360g, 94%). MS (ESI) for  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O} \cdot (\text{HCl})_2 (\text{MH})^+ m/z = 270$ .

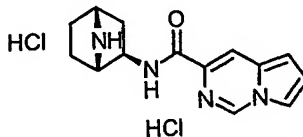
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**Example 4:** *N*-[(3*R*,4*S*)-1-azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide fumarate:



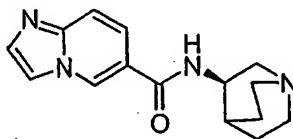
To a stirred solution of pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride (202 mg, 1.02 mmol) in DMF (10 mL) is added DIEA (717  $\mu\text{L}$ , 4.12 mmol) and *exo*-[2.2.1]-Amine (456 mg, 1.00 mmol). The mixture is cooled to  $-10^\circ\text{C}$ , and HATU (386 mg, 1.02 mmol) is added in one portion. The reaction mixture is allowed to warm to RT and is stirred overnight. The solvent is removed *in vacuo*, and the residue is partitioned between saturated aqueous potassium carbonate solution and  $\text{CHCl}_3$ . The aqueous layer is extracted with  $\text{CHCl}_3$ . The combined organic layers are washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel eluting with  $\text{CHCl}_3$ - $\text{MeOH}-\text{NH}_4\text{OH}$  (89:9:1) to give the product as a yellow oil (226 mg, 88%). The fumaric acid salt is formed and triturated with acetone to yield the desired product (0.237g, 72%) as an off-white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.05, 8.14, 7.77, 7.04-7.03, 6.82, 6.73, 4.31-4.29, 3.76-3.71, 3.55-3.39, 3.30-3.24, 3.07, 2.24-2.16, 1.91-1.84.

**Example 5:** *N*-[(1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]hept-2-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide dihydrochloride:



Pyrrolo[1,2-*c*]pyrimidine-3-carboxylic acid hydrochloride (198 mg, 1.0 mmol) is dissolved in DMF (10 ml) with DIEA (0.52 ml, 3.0 mmol) and 7-aza-[2.2.1]-Amine (233 mg, 1.1 mmol) and cooled to  $0^\circ\text{C}$ . HATU (380 mg, 1.0 mmol) is added

**Example 7:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyridine-7-carboxamide:

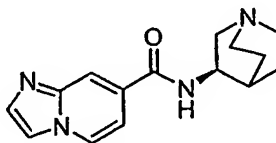


**5 Procedure D:**

A mixture of bromoacetaldehyde diethylacetal (8.0 ml, 52.5 mmol), H<sub>2</sub>O (60 ml), and conc. HCl (2.6 ml) is heated to 90°C with an oil bath for 2 h. 6-aminonicotinic acid (2.5 g, 18.1 mmol) and sodium bicarbonate (4.3 g, 50.7 mmol) are added to the solution at rt, followed by heating the resulting mixture to 60°C with an oil bath for 30 min. Upon cooling to rt a white ppt. is formed. The resulting off white solid is recrystallized from H<sub>2</sub>O/EtOH/Et<sub>2</sub>O to afford white crystals (2.3 g, 10.6 mmol, 59%) for imidazo[1,2-*a*]pyridine-6-carboxylic acid. HRMS (FAB) calcd for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>+H 163.0508, found 163.0492.

Example 7 is prepared following Procedure C. The brown oil is purified with DOWEX 50WX2-400 ion-exchange resin, and the solvent is removed under vacuum. Crystals form upon sitting and are filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> to give (0.24 g, 0.9 mmol, 42%). HRMS (FAB) calcd for C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O+H 271.1559, found 271.1562.

**Example 8:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyridine-7-carboxamide:



7-Methylimidazo[1,2-*a*]pyridine is prepared using Procedure D to give a brown oil (2.8 g, 18.6 mmol, 67%). This compound is used without further purification. HRMS (FAB) calcd for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>+H 133.0766, found 133.0762.

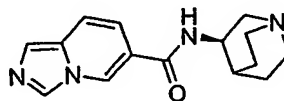
To a 50 ml capacity high-pressure reactor containing 7-methylimidazo[1,2-*a*]pyridine (1.0 g, 6.7 mmol), KOH (5.1 g, 90.7 mmol), and 18-crown-6 (0.3 g, 1.2 mmol) is added DME (15 ml). The mixture is stirred at 70°C and 150psi of O<sub>2</sub> for 4 days. The reaction mixture is diluted with H<sub>2</sub>O (15 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 40 ml). The aqueous layer is acidified with conc. HCl and the solvent is removed

under vacuum. The KCl salt crystallized out of the mixture from H<sub>2</sub>O / EtOH / Et<sub>2</sub>O. The filtrate is concentrated to give a brown solid (1.2 g) for imidazo[1,2-a]pyridine-6-carboxylic acid. This compound is used without further purification. HRMS (FAB) calcd for C<sub>8</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>+H 163.0508, found 163.0491.

5        Example 8 is prepared following Procedure C. The brown oil is purified with DOWEX 50WX2-400 ion-exchange resin, followed by the purification by silica gel chromatography (10% MeOH / 79% CH<sub>2</sub>Cl<sub>2</sub> / 1% NH<sub>3</sub>OH) to give a yellow solid (0.06g, 0.2 mmol, 33%). HRMS (FAB) calcd for C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O+H 271.1559, found 271.1568.

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**Example 9:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-*a*]pyridine-6-carboxamide:



To a 250 ml flask containing methyl 6-methylnicotinate (10.0 g, 66 mmol) and  
15    methyltrioxorhenium (VII) (0.083 g, 0.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 ml) is added 30% aqueous H<sub>2</sub>O<sub>2</sub> (12.0 ml, 132 mmol). This solution is heated to 24°C with an oil bath for 6 h. The biphasic reaction mixture is then treated with a catalytic amount of MnO<sub>2</sub> (0.018 g, 0.2 mmol) and stirred until oxygen evolution ceases. Following phase separation, the water layer is extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 ml), and the combined  
20    organic layers are dried (NaSO<sub>4</sub>), filtered, and concentrated under vacuum to give an off-white solid (10.1 g, 60.4 mmol, 91%) for methyl 6-methylnicotinate 1-oxide. HRMS (FAB) calcd for C<sub>8</sub>H<sub>9</sub>NO<sub>3</sub>+H 168.0661, found 168.0651.

A 100 ml flask is charged with acetic anhydride (15 ml) and preheated to 110°C. Methyl 6-methylnicotinate 1-oxide (5.0 g, 29.6 mmol) is added, and the  
25    mixture is stirred at 110°C for 10 min, followed by the reflux at 130°C for 2 h. EtOH (15 ml) is added dropwise to the mixture, and it is refluxed at 80°C for an additional 30 min. After cooling in an ice-water bath, the mixture is poured into H<sub>2</sub>O (30 ml) and neutralized with NaHCO<sub>3</sub>. The resulting mixture is extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 60 ml) and the combined organic layers are dried (NaSO<sub>4</sub>), filtered, and concentrated  
30    under vacuum. The resulting yellow solid is purified by silica gel chromatography (20% EtOAc/Hexanes), followed by recrystallization from hexanes to give yellow a

solid (2.3g, 11.0 mmol, 37%) for methyl 6-[(acetyloxy)methyl]nicotinate. MS (ESI+) for  $C_{10}H_{11}NO_4$   $m/z$  210.2 (M+H)<sup>+</sup>.

A 50 ml flask containing methyl 6-[(acetyloxy)methyl]nicotinate (1.5 g, 7.2 mmol) in  $CH_3OH$  (7.5 ml) is heated to 40°C until the solid completely dissolves. To this solution,  $K_2CO_3$  (0.03 g, 0.2 mmol) is added, and the reaction mixture is stirred at rt for 2 h. The reaction mixture is extracted with  $CH_2Cl_2$  (3 x 15 ml) and the combined organic layers are dried ( $NaSO_4$ ), filtered, and concentrated under vacuum to give a white solid (1.1g, 6.4 mmol, 89%) for methyl 6-(hydroxymethyl)nicotinate. This compound is used without further purification. MS (ESI+) for  $C_8H_9O_3$   $m/z$  168.2 (M+H)<sup>+</sup>.

A 100 ml flask containing methyl 6-(hydroxymethyl)nicotinate (1.1 g, 6.4 mmol), triethylamine (2.7 ml, 19.2 mmol) and  $CH_2Cl_2$  (25 ml) is cooled in an ice-bath to 0°C. Methanesulfonyl chloride (1.0 ml, 12.8 mmol) is added dropwise to the mixture and the mixture is allowed to stir at 0°C for 2 h. The 2.0M  $Na_2CO_3$  (25 ml) is added to the cool solution, and the mixture is diluted with methyl t-butyl ether (50 ml). The mixture is washed with 2.0M  $Na_2CO_3$  (2 x 50 ml) and brine. The ether layer is dried ( $MgSO_4$ ), filtered, and concentrated under vacuum to give an off-white solid (1.5g, 6.4 mmol, 100%) for methyl 6-[[[(methylsulfonyl)oxy]methyl]nicotinate. MS (ESI+) for  $C_9H_{11}O_5S$   $m/z$  246.17 (M+H)<sup>+</sup>.

Methyl 6-[[[(methylsulfonyl)oxy]methyl]-nicotinate (1.5 g, 6.4 mmol),  $NaN_3$  (0.8 g, 12.8 mmol) in dry DMF (30 ml) are heated in an oil-bath to 70°C for 2 h. After the reaction mixture is cooled to rt it is diluted with EtOAc (30 ml) and extracted with  $H_2O$  (5 x 50 ml). The EtOAc layer is dried ( $MgSO_4$ ), filtered, and concentrated under vacuum to give an orange oil, which is purified by silica gel chromatography ( $CH_2Cl_2$ ) to give a yellow solid (0.65 g, 2.7 mmol, 42%) for methyl 6-(azidomethyl)nicotinate. HRMS (FAB) calcd for  $C_8H_8N_4O_2+H$  193.0726, found 193.0718.

To a 50 ml flask containing methyl 6-(azidomethyl)nicotinate (0.22 g, 1.2 mmol) and 10 % palladium on charcoal (0.12 g, 0.1 mmol) is added MeOH (18 ml) and conc. HCl (0.3 ml). The mixture is hydrogenated at rt and balloon pressure, until no more hydrogen is consumed (about 2 h). The reaction mixture is filtered through a pad of Celite, and the solvent is removed in vacuum to give a yellow solid (0.25 g, 1.0 mmol, 87%) for methyl 6-(aminomethyl)nicotinate. This compound is used without

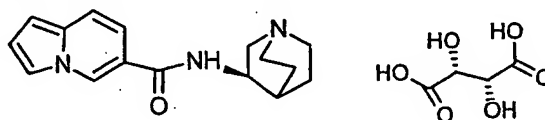
further purification. HRMS (FAB) calcd for  $C_8H_{10}N_2O_2 + H$  167.0820, found 167.0804.

The methyl imidazo[1,5-a]pyridine-6-carboxylate is prepared using Procedure A to give a yellow solid which is purified by silica gel chromatography (EtOAc) to give a yellow solid (0.13 g, 0.7 mmol, 71%). HRMS (FAB) calcd for  $C_9H_8N_2O_2 + H$  177.0664, found 177.0657.

Imidazo[1,5-a]pyridine-6-carboxylic acid is prepared using Procedure B to give a yellow solid which is recrystallized from  $H_2O/EtOH/Et_2O$  to afford an off-white crystals (0.1 g, 0.5 mmol, 71%). HRMS (FAB) calcd for  $C_8H_6N_2O_2 + H$  163.0508, found 163.0502.

Example 9 is prepared using Procedure C. The brown oil is purified with DOWEX 50WX2-400 ion-exchange resin, followed by the purification by silica gel chromatography (10% MeOH / 79%  $CH_2Cl_2$  / 1%  $NH_3OH$ ) to give yellow solid (0.1 g, 0.36 mmol, 93%). HRMS (FAB) calcd for  $C_{15}H_{18}N_4O + H$  271.1559, found 271.1554.

**Example 10:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide tartrate:



To a sealed tube containing ethyl 6-chloronicotinate (2.0 g, 10.8 mmol),  $CuI$  (0.3 g, 1.6 mmol, 15 mol%),  $Pd(PPh_3)_2Cl_2$  (0.4 g, 0.5 mmol, 5 mol%), anhydrous  $Et_3N$  (60 ml) is added prop-1-yne (7.0 ml, 129 mmol). The mixture is allowed to stir at 60°C for 3 h. The mixture is filtered through a pad of celite and solvent is removed in vacuum. The resulting solid is purified by silica gel chromatography (30% EtOAc/Hexanes) to give a yellow solid (1.3 g, 6.8 mmol, 63%) for ethyl 6-prop-1-ynynicotinate: HRMS (EI) calcd for  $C_{11}H_{11}O_2$  189.0790, found 189.0787.

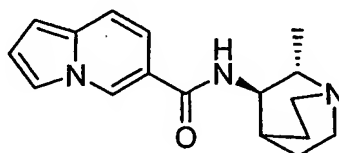
Ethyl indolizine-6-carboxylate is prepared according to Kel'in, A. V., et al, *J. Am. Chem. Soc.* 2001, 123, 2074-5. Yield 20%. HRMS (EI) calcd for  $C_{11}H_{11}O_2$  189.0790, found 189.0786.

To ethyl indolizine-6-carboxylate (0.5 g, 2.7 mmol) in EtOH (8.0 ml) and  $H_2O$  (1.0 ml) is added KOH (1.5 g, 2.7 mmol). The mixture is stirred at rt for 1 h. The reaction mixture is diluted with  $H_2O$  (10 ml) and extracted with  $CH_2Cl_2$  (2 x 15 ml). The aqueous layer is acidified with 5N HCl and extracted with  $CH_2Cl_2$  (2 x 15 ml),

dried (MgSO<sub>4</sub>), filtered, and concentrated to give a yellow solid (0.4 g, 2.5 mmol, 93%) for indolizine-6-carboxylic acid: HRMS (EI) calcd for C<sub>9</sub>H<sub>7</sub>O<sub>2</sub> 161.0477, found 161.0477.

To a solution of indolizine-6-carboxylic acid (0.4 g, 2.5 mmol) in THF (20 ml) is added (3*R*)-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (0.5 g, 2.5 mmol) and DIEA (0.6 ml, 15.0 mmol). The reaction mixture is cooled to 0°C and HATU (1.0 g, 2.5 mmol) is added to it. The mixture is allowed to stir at rt for 3 h. The reaction mixture is diluted with 1N NaOH (20 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 ml), dried over MgSO<sub>4</sub>, filtered, and concentrated. The resulting solid is purified by silica gel chromatography (10% MeOH / 89% CH<sub>2</sub>Cl<sub>2</sub> / 1% NH<sub>3</sub>OH) to give an off white solid (0.4 g, 1.5 mmol, 59%). The resulting solid (0.2 g, 0.7 mmol) is dissolved in MeOH (2 ml) and a solution of d-tartaric acid (0.1 g, 0.7 mmol) in MeOH (2 ml) is added to it. The solvent is removed under vacuum and resulting solid is recrystallized from MeOH / Et<sub>2</sub>O to give an off white solid (0.1 g, 0.2 mmol, 29%): HRMS (FAB) calcd for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O+H 270.1606, found 270.1604.

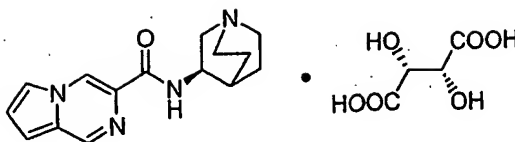
**Example 11:** *N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide tartrate:



Example 11 is prepared following Procedure A starting from indolizine-6-carboxylic acid and 2-methyl quinuclidine. The resulting solid is purified by silica gel chromatography (10% MeOH / 89% CH<sub>2</sub>Cl<sub>2</sub> / 1% NH<sub>3</sub>OH) to give yellow solid, which is dissolved in MeOH (2 ml) and a solution of d-tartaric acid (0.1 g, 0.7 mmol) in MeOH (2 ml) is added to it. The solvent is removed under vacuum and resulting solid is recrystallized from MeOH / Et<sub>2</sub>O to give a yellow solid (0.17 g, 0.4 mmol, 67%): HRMS (FAB) calcd for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O+H 284.1763, found 284.1758.

**Example 12:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide tartrate:



**Procedure E:**

Pyrrole-2-carboxaldehyde (recrystallized from EtOAc/hexanes prior to use) (3.67 g, 38.6 mmol) is added to a solution of ethyl 3-ethoxy-O-ethylserinate (7.95 g, 38.6 mmol) in freshly distilled THF or CH<sub>2</sub>Cl<sub>2</sub> (100 mL) in an oven dried 250 mL flask. 3Å activated molecular sieves (approximately 1/3 the volume of the reaction vessel) are added, and the resulting mixture is allowed to stir under nitrogen until the starting pyrrole-2-carboxaldehyde is consumed as determined by <sup>1</sup>H NMR. The reaction mixture is filtered through a pad of celite, and the solvent removed *in vacuo* to give an orange oil (9.59 g) for ethyl 3-ethoxy-O-ethyl-N-(1*H*-pyrrol-2-ylmethylene)serinate that is used without purification: MS (ESI+) for C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> *m/z* 282.96 (M+H)<sup>+</sup>.

**Procedure F:**

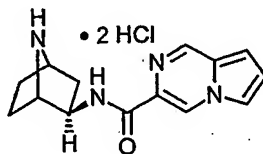
To a hot (65°C) solution of TFA (44 mL, 510 mmol) and phosphorus oxychloride (39.0 g, 140 mmol) is added drop-wise a solution of ethyl 3-ethoxy-O-ethyl-N-(1*H*-pyrrol-2-ylmethylene)serinate (Dekhane, M; Potier, P; Dodd, R. H. *Tetrahedron*, 49, 1993, 8139-46.) (9.6 g, 28.0 mmol) in anhydrous 1,2-dichloroethane (200 mL). The black mixture is allowed to stir at 65°C for 18 h at which point it is cooled to rt and neutralized with sat. NaHCO<sub>3</sub> and solid NaHCO<sub>3</sub> to pH ~ 9. The phases are separated and the basic phase extracted with EtOAc (4 x 100 mL). The organic phases are combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give a black oil that is purified with silica gel chromatography (35% EtOAc/heptanes to 50% over several liters) to give a light brown solid for ethyl pyrrolo[1,2-*a*]pyrazine-3-carboxylate. Yield 24%. HRMS (FAB) calcd for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>+H 191.0820, found 191.0823.

Pyrrolo[1,2-*a*]pyrazine-3-carboxylic acid hydrochloride is prepared from ethyl pyrrolo[1,2-*a*]pyrazine-3-carboxylate, using Procedure B to give a pale brown solid. Yield 90%. HRMS (FAB) calcd for C<sub>8</sub>H<sub>6</sub>O<sub>2</sub>N<sub>2</sub>+H 163.0508, found 163.0513,

Example 12 is prepared using Procedure C to give a solid purified by silica gel chromatography (9% MeOH/1% NH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> as the eluent) salted with d-tartaric

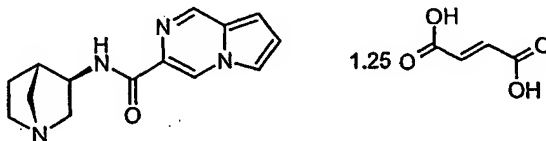
acid, and crystallized from IPA/Et<sub>2</sub>O to give a white powder. Yield 43%. HRMS (FAB) calcd for C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O+H 271.1559, found 271.1547.

**Example 13:** *Exo-N-[(2R)-7-azabicyclo[2.2.1]hept-2-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide dihydrochloride:*



Pyrrolo[1,2-a]pyrazine-3-carboxylic acid hydrochloride (200 mg, 1.0 mmol) is dissolved in DMF (10 ml) with DIEA (0.52 ml, 3.0 mmol) and *tert*-butyl (2*R*)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate (233 mg, 1.1 mmol) and cooled to 0°C. HATU (380 mg, 1.0 mmol) is added portionwise, and the reaction stirred overnight at rt, allowing the ice bath to expire. Volatiles are removed *in vacuo*, and the crude material is chromatographed over 25 g slurry-packed silica, eluting with 50% EtOAc/hexane. The appropriate fractions are collected and concentrated to a tan solid. The solid residue is dissolved in 3M HCl in MeOH (5 ml) and MeOH (5 ml) and stirred overnight. Slight heating is required at 40°C. Volatiles are again removed *in vacuo*, and the residue is treated with IPA (2 ml) and Et<sub>2</sub>O (2 ml). The resulting precipitate is isolated via filtration, rinsed with Et<sub>2</sub>O, and dried to afford 239 mg (73%) as a yellow solid. MS (ESI<sup>+</sup>) for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O. 2 HCl *m/z*: 257.1 (M+H)<sup>+</sup>.

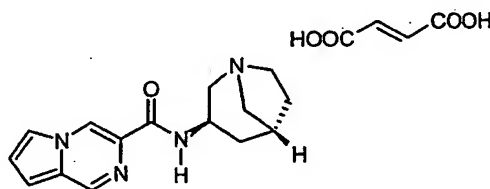
**Example 14:** *N-[(3R,4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide•1.25 fumarate:*



To a stirred solution of pyrrolo[1,2-a]pyrazine-3-carboxylic acid (237 mg, 1.07 mmol) in dry DMF (10 mL) are added DIEA (531 μL, 3.05 mmol) and (3*R*,4*S*)-1-azabicyclo[2.2.1]heptan-3-amine bis(hydro-*para*-toluenesulfonate) (456 mg, 1.00 mmol). The mixture is cooled to 0 °C, and HATU (380 mg, 1.00 mmol) is added in one portion. The reaction mixture is allowed to warm to rt and stir overnight. The solvent is removed *in vacuo*, and the residue is partitioned between saturated aqueous potassium carbonate solution and CHCl<sub>3</sub>. The aqueous layer is extracted with CHCl<sub>3</sub>

(2X). The combined organic layers are washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH (90:9:1) gave the product as a white solid (255 mg, 99%). To a stirred solution of the amide (255 mg, 0.99 mmol) in MeOH (5 mL) is added a warm solution of fumaric acid (115 mg, 0.99 mmol) in methanol (5 mL). The mixture is warmed to 38 °C for 10 min. The solvent is removed *in vacuo* and the remaining residue is diluted with acetone (10 mL). The mixture is stirred overnight at rt. The solid precipitate is collected by filtration, washed with acetone, and dried under high vacuum overnight to give 322 mg (78%) of Example 14 as a white solid: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.89, 8.81, 7.84, 7.05, 7.01, 6.71, 4.26, 3.73-3.67, 3.51-3.21, 3.07, 2.23-2.16, 1.89-1.82.

**Example 15:** *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide fumurate:

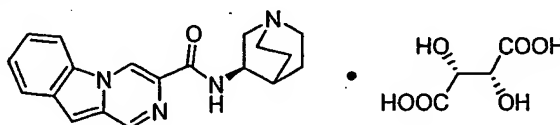


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Example 15 is prepared from pyrrolo[1,2-*a*]pyrazine-3-carboxylic acid hydrochloride and (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine dihydrochloride using Procedure C to give a mixture purified by silica gel chromatography (9% MeOH/1%NH<sub>3</sub>OH/CHCl<sub>3</sub> as the eluent) salted with fumaric acid, and crystallized from acetone to give a white solid. Yield 83%. HRMS (FAB) calcd for C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O MH<sup>+</sup> 271.1559, found 271.1550.

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**Example 16:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]pyrazino[1,2-*a*]indole-3-carboxamide tartrate:



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To a suspension of lithium aluminum hydride (10.6g, 264 mmol) in THF (200 mL) is added dropwise a solution of ethyl indole-2-carboxylate (50.0 g, 256 mmol) in THF (250 mL) over 25 minutes. After 3 h, water (10.6 mL) is carefully added,

followed by 15% NaOH (10.6 mL), followed by additional portion of water (31.8 mL). The resulting suspension is dried ( $\text{Na}_2\text{SO}_4$ ) and filtered through celite. After concentration under reduced pressure, the white solid (34.0 g) is crystallized from EtOAc/hexanes to give white needles for 1*H*-indol-2-ylmethanol. Yield 83%. HRMS (FAB) calcd for  $\text{C}_9\text{H}_9\text{NO}+\text{H}$  148.0762, found 148.0771.

1*H*-Indole-2-carbaldehyde is prepared according to Berccalli, E. M., et al, *J. Org. Chem.* 2000, 65, 8924-32, and crystallized from EtOAc/hexanes to give a yellow/brown plates. Yield 81%. MS (ESI+) for  $\text{C}_9\text{H}_7\text{NO}$   $m/z$  146.1 ( $\text{M}+\text{H}$ )<sup>+</sup>.

Ethyl 3-ethoxy-O-ethyl-N-(1*H*-indol-2-ylmethylene)serinate is prepared using Procedure E to give an orange oil. Yield 94%. MS (ESI+) for  $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4$   $m/z$  333.8 ( $\text{M}+\text{H}$ )<sup>+</sup>.

#### Procedure G:

Ethyl 9*H*-beta-carboline-3-carboxylate and ethyl pyrazino[1,2-*a*]indole-3-carboxylate are prepared according to Dekhane, M., et al, *Tetrahedron*, 49, 1993, 8139-46, to give a dark colored solid that is purified with silica gel chromatography (20% to 75% EtOAc/hexanes as the eluent) to give the ethyl 9*H*-beta-carboline-3-carboxylate as a brown solid (yield 16%) and the ethyl pyrazino[1,2-*a*]indole-3-carboxylate as a brown solid (yield 35%). Ethyl 9*H*-beta-carboline-3-carboxylate; MS (ESI+) for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$   $m/z$  241.10 ( $\text{M}+\text{H}$ )<sup>+</sup>; MS (ESI-) for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$   $m/z$  239.15 ( $\text{M}-\text{H}$ )<sup>-</sup>.

#### Procedure H:

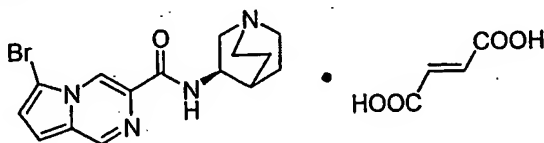
To a solution of ethyl pyrazino[1,2-*a*]indole-3-carboxylate (0.49 g, 2.0 mmol) in EtOH (30 mL) is added crushed potassium hydroxide (1.1 g, 20.0 mmol) followed by water (30 mL). The resulting dark colored solution is stirred at rt for 40 min and then neutralized with conc. HCl to pH ~2. The acidic mixture is concentrated to dryness to afford pyrazino[1,2-*a*]indole-3-carboxylic acid hydrochloride. HRMS (FAB) calcd for  $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2+\text{H}$  213.0664, found 213.0658.

Example 16 is prepared from pyrazino[1,2-*a*]indole-3-carboxylic acid hydrochloride using Procedure C to give a solid purified by silica gel chromatography (4% MeOH/1%  $\text{NH}_3\text{OH}/\text{CH}_2\text{Cl}_2$  as the eluent) salted with d-tartaric acid, and

crystallized from EtOH/Et<sub>2</sub>O to give a white powder. Yield 34%. HRMS (FAB) calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O+H 321.1715, found 321.1700.

**Example 17:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*a*]pyrazine-3-

5 carboxamide fumurate:

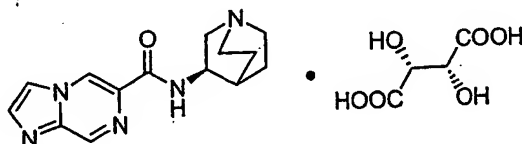


To a solution of ethyl pyrrolo[1,2-*a*]pyrazine-3-carboxylate (0.60 g, 3.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) is added *N*-bromosuccinimide (0.56 g, 3.18 mmol) in one portion. After 1 h, solvent is removed *in vacuo* and the crude solid purified using preparative HPLC (1% IPA/heptane (0-5 minutes) to 2% isocratic) to give a brown solid for ethyl 6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxylate. Yield 57%. MS (ESI+) for C<sub>10</sub>H<sub>9</sub>BrN<sub>2</sub>O<sub>2</sub> *m/z* 271.01 (M+H)<sup>+</sup>.

Ethyl 6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxylate is prepared from ethyl 6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxylate using Procedure H to give a dark colored solid that is used without purification; MS (ESI+) for C<sub>8</sub>H<sub>5</sub>BrN<sub>2</sub>O<sub>2</sub> *m/z* 241.01 (M+H)<sup>+</sup>.

To a suspension of 6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxylic acid hydrochloride (1.67 mmol), (*R*)-3-aminoquinulidine dihydrochloride (0.34 g, 1.67 mmol), DIEA (1.5 mL, 8.35 mmol) in DMF (20 mL) and THF (10 mL) is added HATU (0.64 g, 1.67 mmol). The resulting suspension is stirred for 16 h at which time it is concentrated to dryness under reduced pressure. The resulting material is absorbed to silica gel and purified with silica gel chromatography (9% MeOH/1%NH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> as the eluent) salted with fumaric acid, and crystallized from EtOH/acetone/Et<sub>2</sub>O to give an off white spheres. Yield 45%. HRMS (FAB) calcd. for C<sub>15</sub>H<sub>17</sub>BrN<sub>4</sub>O+H 349.0664, found 349.0647.

**Example 18:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*a*]pyrazine-6-carboxamide tartrate:



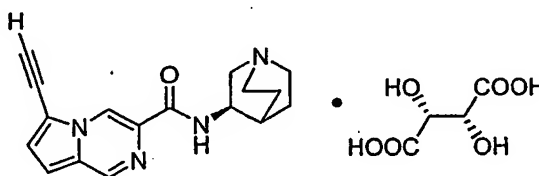
Ethyl 3-ethoxy-O-ethyl-N-(1*H*-imidazol-2-ylmethylene)serinate is prepared from imidazole-2-carboxaldehyde as a yellow solid using Procedure E with the exception that EtOH and CH<sub>2</sub>Cl<sub>2</sub> (1:1) are substituted as reaction solvents. Yield 88%. MS (ESI+) for C<sub>13</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> *m/z* 284.33 (M+H)<sup>+</sup>:

5 Ethyl imidazo[1,2-*a*]pyrazine-6-carboxylate is prepared from ethyl 3-ethoxy-O-ethyl-N-(1*H*-imidazol-2-ylmethylene)serinate using Procedure G to give a black oil that is purified by preparative HPLC (1% IPA/heptane (0-5 minutes) to 2% isocratic) that gives the product as a yellow solid. Yield 6%. MS (ESI+) for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub> *m/z* 192.13 (M+H)<sup>+</sup>.

10 Imidazo[1,2-*a*]pyrazine-6-carboxylic acid hydrochloride is prepared from ethyl imidazo[1,2-*a*]pyrazine-6-carboxylate using Procedure B to give a pale brown solid that is utilized without further purification; MS (ESI+) for C<sub>7</sub>H<sub>5</sub>N<sub>3</sub>O<sub>2</sub> *m/z* 164.9 (M+H)<sup>+</sup>.

Example 18 is prepared from imidazo[1,2-*a*]pyrazine-6-carboxylic acid  
15 hydrochloride using Procedure C to give a solid purified by silica gel chromatography (9% MeOH/1%NH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> as the eluent) salted with d-tartaric acid, and crystallized from IPA/Et<sub>2</sub>O to give a white powder. Yield 90% over 2 steps. HRMS calcd for C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>O<sub>1</sub>+H 272.1511, found 272.1503.

20 **Example 19:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-ethynylpyrrolo[1,2-*a*]pyrazine-3-carboxamide tartrate:

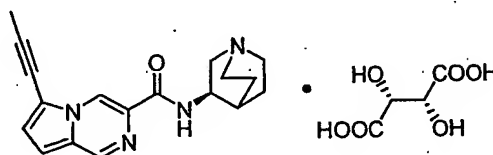


To a degassed solution of *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxamide (0.59 g, 1.7 mmol), triethylamine (5.8  
25 mL, 42.2 mmol) in dioxane (10 mL) is added copper(I) iodide (0.09 g, 0.50 mmol), (triisopropylsilyl) acetylene (1.54 g, 8.5 mmol), and dichlorobis(triphenylphosphine) palladium(II) (0.12 g, 0.17 mmol). The resulting mixture is stirred at 80°C for 18 h, cooled to rt, and concentrated to dryness. The residue is taken up in CHCl<sub>3</sub> and washed with a solution of 1:1 NH<sub>4</sub>OH/brine (3 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered,  
30 and concentrated to dryness. The resulting material is purified with preparative HPLC

to give a colored oil. Yield 60%. HRMS (FAB) calcd for  $C_{26}H_{38}N_4OSi+H$  451.2893, found 451.2872.

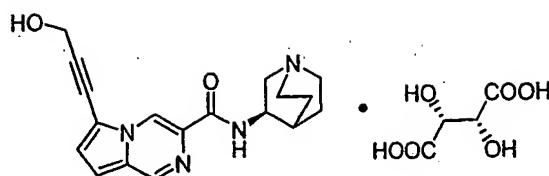
To a solution of *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-  
 [(triisopropylsilyl)ethynyl] pyrrolo[1,2-*a*]pyrazine-3-carboxamide (0.45 g, 1.0 mmol)  
 5 in THF (40 mL) is added a 1.0 M solution of tetrabutylammonium fluoride in THF  
 (4.0 mL). The resulting solution is allowed to stir for 20 minutes at which point it is  
 concentrated to dryness and absorbed to silica gel and purified with silica gel  
 chromatography (5% MeOH/ 1%  $NH_3OH/CH_2Cl_2$  to 10% as the eluent) salted with d-  
 tartaric acid, and crystallized from EtOH/Et<sub>2</sub>O to give a pale brown solid. Yield 98%.  
 10 HRMS (FAB) calcd for  $C_{17}H_{18}N_4O+H$  295.1559, found 295.1566.

**Example 20:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-prop-1-ynylpyrrolo[1,2-  
*a*]pyrazine-3-carboxamide tartrate:



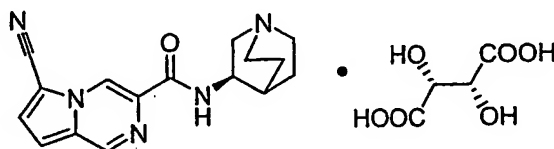
15 To an argon purged mixture of dichlorobis(benzonitrile)palladium (II) (0.085  
 g, 0.22 mmol) and copper (I) iodine (0.124 g, 0.65 mmol) is added, *N*-[(3*R*)-1-  
 azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxamide (0.641 g,  
 1.8 mmol) and dioxane (20 mL). The suspension is sparged with argon, and  
 diisopropylamine (0.30 mL, 1.5 mmol), tri tert-butyl phosphine (0.064 g, 0.32 mmol)  
 20 and condensed propyne (excess) is added. The reaction vessel is quickly sealed and  
 stirred at rt for 15 h at which point it is filtered through a plug of celite, concentrated  
 to dryness, and the residue dissolved in  $CHCl_3$  (150 mL) that is washed with a  
 solution containing 1:1  $NH_4OH$ /brine (5 x 35 mL). The crude oil is purified using  
 preparative HPLC to give a yellow oil that is salted with d-tartaric acid, and  
 25 crystallized from EtOH/Et<sub>2</sub>O to give a pale yellow solid. Yield 5%. HRMS (FAB)  
 calcd for  $C_{18}H_{20}N_4O+H$  309.1715, found 309.1715.

**Example 21:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo  
 [1,2-*a*]pyrazine-3-carboxamide tartrate:



To an argon sparged solution of *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxamide (0.230 g, 0.92 mmol), triethylamine (3.2 mL, 23.0 mmol) in dioxane (5 mL) is added copper (I) iodine (0.054 g, 0.28 mmol), propargyl alcohol (0.22 mL, 3.68 mmol), and dichlorobis(triphenylphosphino)-palladium (II) (0.063 g, 0.09 mmol). The reaction vessel is purged with argon, and stirred at 80°C for 20 h at which point it is filtered through a plug of celite, concentrated to dryness, and the residue dissolved in CHCl<sub>3</sub> (150 mL) that is washed with a solution containing 1:1 NH<sub>4</sub>OH/brine (5 x 35 mL). The residue is purified using silica gel chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> gradient up to 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a pale orange colored oil that is salted with d-tartaric acid, and crystallized from EtOH/Et<sub>2</sub>O to give a tan solid. Yield 24%. HRMS (FAB) calcd for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>+H 325.1664, found 325.1664.

**Example 22:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-cyanopyrrolo[1,2-*a*]pyrazine-3-carboxamide tartrate:



To an argon sparged solution of *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*a*]pyrazine-3-carboxamide (0.77 g, 2.14 mmol) in DMF (25 mL) is added zinc cyanide (0.26 g, 2.20 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.25 g, 0.21 mmol). The resulting suspension is stirred at 95°C for 48 h, then filtered through a pad of celite. The residue is purified using preparative chromatography (carried out on a Chiral OD column using a 40% IPA/heptanes each containing 0.1% diethylamine) to give a pale yellow oil that is salted with d-tartaric acid and crystallized from EtOH/Et<sub>2</sub>O to give a pale yellow solid. Yield 47%. HRMS (FAB) calcd for C<sub>16</sub>H<sub>17</sub>N<sub>5</sub>O+H 296.1511, found 296.1520.



The following compounds are made from the corresponding carboxylic acids following the procedure in Example 2, making non-critical variations.

**Example 23:** 7-Chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-  
c]pyrimidine-3-carboxamide hydrochloride. Yield 70%. HRMS (FAB) calcd for  
5  $C_{16}H_{19}ClN_4O+H$  319.1325, found 319.1322.

**Example 24:** 6-Chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-  
c]pyrimidine-3-carboxamide hydrochloride. Yield 73%. HRMS (FAB) calcd for  
 $C_{16}H_{19}ClN_4O+H$  319.1325, found 319.1318.

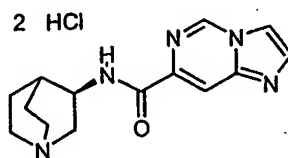
**Example 25:** *N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-  
a]pyrazine-3-carboxamide hydrochloride. Yield 50%. HRMS (FAB) calcd for  
10  $C_{16}H_{20}N_4O+H$  284.1637, found 284.1635.

**Example 26:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-chloropyrrolo[1,2-*c*]pyrimidine-  
3-carboxamide hydrochloride. Yield 63%. HRMS (FAB) calcd for  $C_{15}H_{17}ClN_4O+H$   
305.1169, found 305.1175.

**Example 27:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloropyrrolo[1,2-*c*]pyrimidine-  
3-carboxamide hydrochloride. Yield 39%. HRMS (FAB) calcd for  $C_{15}H_{17}ClN_4O+H$   
305.1169, found 305.1175.

**Example 28:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-*c*]pyrimidine-  
3-carboxamide dihydrochloride. Yield 60%. HRMS (FAB) calcd for  
20  $C_{15}H_{17}BrN_4O+H$  349.0664, found 349.0664.

**Example 29:** *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-*c*]pyrimidine-7-  
carboxamide dihydrochloride:

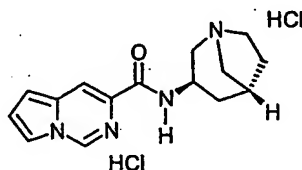


25 To a suspension of imidazole-2-carboxaldehyde (2.3g, 23.4mmol) in 50mL  
dioxane is added to ethyl isocyanoacetate (2.9g, 25.8mmol) and DBU (3.9g,  
25.8mmol). After stirring at RT for 5 days, the reaction is neutralized with 10%  
AcOH. The solvent is removed *in vacuo*. The residue is taken up in EtOAc/H<sub>2</sub>O, the  
aqueous layer is extracted with CHCl<sub>3</sub>, dried (MgSO<sub>4</sub>), filtered and concentrated. The  
30 residue is purified by chromatography (Biotage 40M, eluting with 5% MeOH/EtOAc).

Ethyl imidazo[1,2-c]pyrimidine-7-carboxylate is obtained (1.4g, 32%) as an off-white solid.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  9.14, 8.43, 7.88, 7.81, 4.54-4.48, 1.49-1.44.

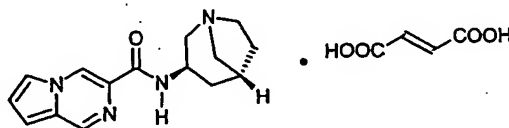
Ethyl imidazo[1,2-c]pyrimidine-7-carboxylate (0.50g, 2.6mmol) and (3*R*)-1-azabicyclo[2.2.2]octan-3-amine are heated under reflux in 5mL EtOH. After 36 h, the solvent is removed. The residue is purified by chromatography (Biotage 40S, 90:9:1  $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ ), the hydrochloride salt is prepared and recrystallized from MeOH/EtOAc to provide 0.377g (42%) of the product. HRMS (FAB) calcd for  $\text{C}_{14}\text{H}_{17}\text{N}_5\text{O}+\text{H}$  271.1433, found 271.1428.

10 **Example 30:** *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*c*]pyrimidine-3-carboxamide dihydrochloride:



Example 30 is prepared by coupling *exo*-[3.2.1]-Amine using the coupling procedures described for Example 2. The free base is treated with MeOH/HCl, evaporated, triturated ( $\text{EtOH}/\text{Et}_2\text{O}$ ) and dried *in vacuo* to afford Example 30 as a solid. Yield 94%. MS (EI)  $m/z$  270 ( $\text{M}^+$ ).

**Example 31:** *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-*a*]pyrazine-3-carboxamide fumurate:



Example 31 is prepared by coupling *exo*-[3.2.1]-Amine using the coupling procedures described in Example 2. The free base is treated with EtOH and fumaric acid (1.0 eq) and evaporated. The residue is crystallized (acetone) and dried *in vacuo* to afford a white solid. Yield 83%. MS (CI)  $m/z$  271 ( $\text{MH}^+$ ).

### Materials and Methods for Determining $\alpha 7$ nAChR Agonist Activity

#### Cell-based Assay for Measuring the $\text{EC}_{50}$ of $\alpha 7$ nAChR Agonists

Construction and expression of the  $\alpha 7$ -5HT<sub>3</sub> receptor:

The cDNA encoding the N-terminal 201 amino acids from the human  $\alpha 7$  nAChR that contain the ligand binding domain of the ion channel was fused to the  
5 cDNA encoding the pore forming region of the mouse 5HT<sub>3</sub> receptor as described by Eisele JL, et al., Chimaeric nicotinic-serotonergic receptor combines distinct ligand binding and channel specificities, Nature (1993), Dec. 2;366(6454):479-83, and modified by Groppi, et al., WO 00/73431. The chimeric  $\alpha 7$ -5HT<sub>3</sub> ion channel was inserted into pGS175 and pGS179 which contain the resistance genes for G-418 and  
10 hygromycin B, respectively. Both plasmids were simultaneously transfected into SH-EP1 cells and cell lines were selected that were resistant to both G-418 and hygromycin B. Cell lines expressing the chimeric ion channel were identified by their ability to bind fluorescent  $\alpha$ -bungarotoxin on their cell surface. The cells with the highest amount of fluorescent  $\alpha$ -bungarotoxin binding were isolated using a  
15 Fluorescent Activated Cell Sorter (FACS). Cell lines that stably expressed the chimeric  $\alpha 7$ -5HT<sub>3</sub> were identified by measuring fluorescent  $\alpha$ -bungarotoxin binding after growing the cells in minimal essential medium containing nonessential amino acids supplemented with 10% fetal bovine serum, L-glutamine, 100 units/ml penicillin/streptomycin, 250 ng/ml fungizone, 400  $\mu$ g/ml hygromycin B, and 400  
20  $\mu$ g/ml G-418 at 37° C with 6% CO<sub>2</sub> in a standard mammalian cell incubator for at least 4 weeks in continuous culture.

Assay of the activity of the chimeric  $\alpha 7$ -5HT<sub>3</sub> receptor

To assay the activity of the  $\alpha 7$ -5HT<sub>3</sub> ion channel, cells expressing the channel  
25 were plated into each well of either a 96 or 384 well dish (Corning #3614) and grown to confluence prior to assay. On the day of the assay, the cells were loaded with a 1:1 mixture of 2 mM Calcium Green 1, AM (Molecular Probes) dissolved in anhydrous DMSO and 20% pluronic F-127 (Molecular Probes). This solution was added directly to the growth media of each well to achieve a final concentration 2  $\mu$ M. The cells  
30 were incubated with the dye for 60 min at 37° C and then washed with a modified version of Earle's balanced salt solution (MMEBSS) as described in WO 00/73431. The ion conditions of the MMEBSS was adjusted to maximize the flux of calcium ion through the chimeric  $\alpha 7$ -5HT<sub>3</sub> ion channel as described in WO 00/73431. The

activity of compounds on the chimeric  $\alpha 7$ -5HT<sub>3</sub> ion channel was analyzed on FLIPR. The instrument was set up with an excitation wavelength of 488 nanometers using 500 milliwatts of power. Fluorescent emission was measured above 525 nanometers with an appropriate F-stop to maintain a maximal signal to noise ratio. Agonist activity of each compound was measured by directly adding the compound to cells expressing the chimeric  $\alpha 7$ -5HT<sub>3</sub> ion channel and measuring the resulting increase in intracellular calcium that is caused by the agonist-induced activation of the chimeric ion channel. The assay is quantitative such that concentration-dependent increase in intracellular calcium is measured as concentration-dependent change in Calcium Green fluorescence. The effective concentration needed for a compound to cause a 50% maximal increase in intracellular calcium is termed the EC<sub>50</sub>. The examples were tested and have EC<sub>50</sub> values from about 125 nM to about 11,109 nM.

#### Binding Constants:

Another way for measuring  $\alpha 7$  nAChR agonist activity is to determine binding constants of a potential agonist in a competition binding assay. For  $\alpha 7$  nAChR agonists, there is good correlation between functional EC<sub>50</sub> values using the chimeric  $\alpha 7$ -5HT<sub>3</sub> ion channel as a drug target and binding affinity of compounds to the endogenous  $\alpha 7$  nAChR.

#### Membrane Preparation.

Male Sprague-Dawley rats (300-350g) are sacrificed by decapitation and the brains (whole brain minus cerebellum) are dissected quickly, weighed and homogenized in 9 volumes/g wet weight of ice-cold 0.32 M sucrose using a rotating pestle on setting 50 (10 up and down strokes). The homogenate is centrifuged at 1,000 x g for 10 minutes at 4°C. The supernatant is collected and centrifuged at 20,000 x g for 20 minutes at 4°C. The resulting pellet is resuspended to a protein concentration of 1 - 8 mg/mL. Aliquots of 5 mL homogenate are frozen at -80°C until needed for the assay. On the day of the assay, aliquots are thawed at rt and diluted with Kreb's - 20 mM Hepes buffer pH 7.0 (at rt) containing 4.16 mM NaHCO<sub>3</sub>, 0.44 mM KH<sub>2</sub>PO<sub>4</sub>, 127 mM NaCl, 5.36 mM KCl, 1.26 mM CaCl<sub>2</sub>, and 0.98 mM MgCl<sub>2</sub>, so that 25 - 150  $\mu$ g protein are added per test tube. Proteins are

determined by the Bradford method (Bradford, M.M., *Anal. Biochem.*, 72, 248-254, 1976) using bovine serum albumin as the standard.

#### Binding Assay.

- 5 For saturation studies, 0.4 mL homogenate are added to test tubes containing buffer and various concentrations of radioligand, and are incubated in a final volume of 0.5 mL for 1 hour at 25°C. Nonspecific binding was determined in tissues incubated in parallel in the presence of 0.05 mls MLA for a final concentration of 1  $\mu$ M, added before the radioligand. In competition studies, drugs are added in
- 10 increasing concentrations to the test tubes before addition of 0.05 mls [ $^3$ H]-MLA for a final concentration 3.0 to 4.0 nM. The incubations are terminated by rapid vacuum filtration through Whatman GF/B glass filter paper mounted on a 48 well Brandel cell harvester. Filters are pre-soaked in 50 mM Tris HCl pH 7.0 - 0.05 % polyethylenimine. The filters are rapidly washed two times with 5 mL aliquots of cold
- 15 0.9% saline and then counted for radioactivity by liquid scintillation spectrometry.

#### Data Analysis.

- In competition binding studies, the inhibition constant ( $K_i$ ) was calculated from the concentration dependent inhibition of [ $^3$ H]-MLA binding obtained from non-linear regression fitting program according to the Cheng-Prusoff equation (Cheng,
- 20 Y.C. and Prusoff, W.H., *Biochem. Pharmacol.*, 22, p. 3099-3108, 1973). Hill coefficients were obtained using non-linear regression (GraphPad Prism sigmoidal dose-response with variable slope).

What is claimed:

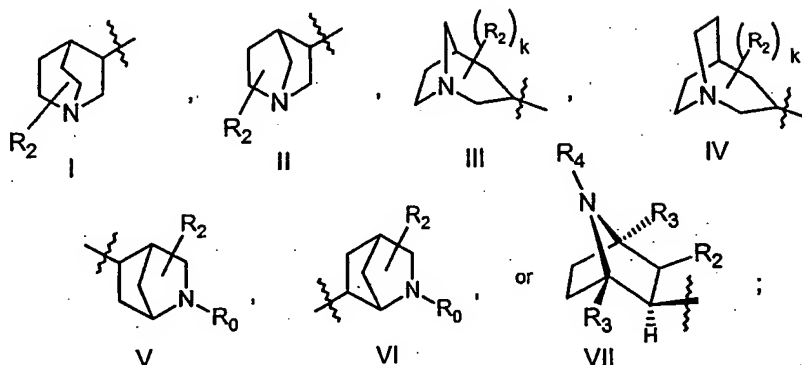
1. A compound of the Formula I:



Formula I

- 5 wherein  $R_1$  is H, alkyl, or haloalkyl;

Azabicyclo is



$R_0$  is H, lower alkyl, lower substituted alkyl, or lower halogenated alkyl;

$R_2$  is H, F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or

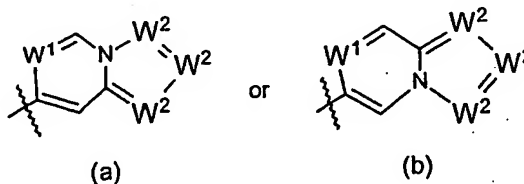
- 10 aryl;

$k$  is 1 or 2, provided that when  $k$  is 2, one  $R_2$  is other than H;

Each  $R_3$  is independently H, alkyl, or substituted alkyl;

$R_4$  is H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, -OH, -CN, -NH<sub>2</sub>, -NH(alkyl), or -N(alkyl)<sub>2</sub>;

- 15 W is



wherein  $W^1$  is N or CH;

Each  $W^2$  is N or C( $R_5$ ), provided that no more than one  $W^2$  is N;

Each  $R_5$  is independently H, alkyl, substituted alkyl, halogenated alkyl,

- 20 alkenyl, substituted alkenyl, halogenated alkenyl, alkynyl, substituted alkynyl, halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N( $R_{10}$ )<sub>2</sub>, -N( $R_{10}$ )<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, aryl,  $R_7$ ,  $R_9$ , or two  $R_5$  on adjacent carbon atoms may combine for W to be a 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally

substituted on the newly formed ring where valency allows with up to 2 substituents independently selected from F, Cl, Br, I, and R<sub>6</sub>;

R<sub>6</sub> is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -NR<sub>8</sub>R<sub>8</sub>, -C(O)R<sub>8</sub>,  
 5 -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>NR<sub>8</sub>R<sub>8</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)NR<sub>8</sub>R<sub>8</sub>, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, phenyl, phenyl having 0-4 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,  
 10 naphthyl, or naphthyl having 0-4 substituents independently selected from F, Cl, Br, I, or R<sub>15</sub>;

R<sub>7</sub> is 5-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms independently selected from the group consisting of -O-, =N-, -N(R<sub>14</sub>)-, and -S-, and having 0-1 substituent selected from R<sub>15</sub>, and further having 0-3  
 15 substituents independently selected from F, Cl, Br, or I, wherein the R<sub>7</sub> moiety attaches to other substituents as defined in formula I at any position as valency allows;

Each R<sub>8</sub> is independently H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl  
 20 substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>;

R<sub>9</sub> is 6-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms selected from =N- and having 0-1 substituent selected from R<sub>15</sub> and 0-3 substituent(s) independently selected from F, Cl, Br, or I, wherein the R<sub>9</sub> moiety attaches to other substituents as defined in formula I at any position as valency  
 25 allows;

Each R<sub>10</sub> is independently H, alkyl, cycloalkyl, heterocycloalkyl, alkyl substituted with 1 substituent selected from R<sub>13</sub>, cycloalkyl substituted with 1 substituent selected from R<sub>13</sub>, heterocycloalkyl substituted with 1 substituent selected from R<sub>13</sub>, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl,  
 30 phenyl, or substituted phenyl;

Each R<sub>11</sub> is independently H, alkyl, cycloalkyl, heterocyclo-alkyl, halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

R<sub>13</sub> is -OR<sub>11</sub>, -SR<sub>11</sub>, -NR<sub>11</sub>R<sub>11</sub>, -C(O)R<sub>11</sub>, -SOR<sub>11</sub>, -SO<sub>2</sub>R<sub>11</sub>, -C(O)NR<sub>11</sub>R<sub>11</sub>,

-CN, -CF<sub>3</sub>, -NR<sub>11</sub>C(O)R<sub>11</sub>, -S(O)<sub>2</sub>NR<sub>11</sub>R<sub>11</sub>, -NR<sub>11</sub>S(O)<sub>2</sub>R<sub>11</sub>, or -NO<sub>2</sub>;

R<sub>14</sub> is independently H, alkyl, halogenated alkyl, limited substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, or substituted heterocycloalkyl;

5 R<sub>15</sub> is alkyl, substituted alkyl, halogenated alkyl, -OR<sub>11</sub>, -CN, -NO<sub>2</sub>, -NR<sub>10</sub>R<sub>10</sub>;

R<sub>16</sub> is H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, phenyl, or phenyl having 0-4 substituents independently selected from F, Cl, Br, I, and R<sub>15</sub>; or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof.

10 2. The compound of claim 1, wherein R<sub>1</sub> is H, lower alkyl, or cycloalkyl.

3. The compound of claim 2, wherein R<sub>2</sub> is H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

4. The compound of claim 3, wherein R<sub>2</sub> is H, or lower alkyl.

5. The compound of claim 4, wherein Azabicyclo is I.

15 6. The compound of claim 5, wherein W<sup>1</sup> is CH.

7. The compound of claim 6, wherein each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>,

20 -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

8. The compound of claim 7, wherein the compound is

25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]indolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-methylindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-chloroindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-bromoindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-cyanoindolizine-6-carboxamide;

30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-ethynylindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroindolizine-6-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoindolizine-6-carboxamide;



- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-methylindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-chloroindolizine-6-carboxamide;  
5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-bromoindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-cyanoindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-ethynylindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]indolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-methylindolizine-7-carboxamide;  
10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-chloroindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-bromoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-1-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylindolizine-7-carboxamide;  
15 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-methylindolizine-7-carboxamide;  
20 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-chloroindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-bromoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
 5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide; any of which is optionally substituted at C-2 having the *S* configuration with methyl, or pharmaceutically acceptable salt thereof.

9. The compound of claim 6, wherein two  $R_5$  on adjacent carbon atoms combine  
 10 for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl,  
 15 -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents  
 20 independently selected from F, Cl, Br, I and R<sub>15</sub>,

wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

25 10. The compound of claim 9, wherein the compound is N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]pyrido[1,2-a]indole-7-carboxamide; N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-9H-carbazole-3-carboxamide; any of which is optionally substituted at C-2 having the *S* configuration with methyl, or pharmaceutically acceptable salt thereof.

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11. The compound of claim 5, wherein W<sup>1</sup> is N.

12. The compound of claim 11, wherein each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted

alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl,  
 5 and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

13. The compound of claim 12, wherein the compound is

- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-  
 15 carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 20 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
 30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-
- 10 carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 15 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-
- 20 carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;
- 30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;
- any of which is optionally substituted at C-2 having the *S* configuration with methyl, or pharmaceutically acceptable salt thereof.

14. The compound of claim 11, wherein two  $R_5$  on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,

wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

15. The compound of claim 14, wherein the compound is  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]pyrazino[1,2-a]indole-3-carboxamide;  
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-9H-beta-carboline-3-carboxamide;  
 any of which is optionally substituted at C-2 having the *S* configuration with methyl, or pharmaceutically acceptable salt thereof.

16. The compound of claim 4, wherein Azabicyclo is II.

17. The compound of claim 16, wherein W<sup>1</sup> is CH.

18. The compound of claim 17, wherein each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

19. The compound of claim 18, wherein the compound is

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]indolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-methylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-chloroindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-bromoindolizine-6-carboxamide;  
5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-cyanoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-ethynylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoindolizine-6-carboxamide;  
10 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-methylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-chloroindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-bromoindolizine-6-carboxamide;  
15 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-cyanoindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-ethynylindolizine-6-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]indolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-methylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-chloroindolizine-7-carboxamide;  
20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-bromoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-1-ethynylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroindolizine-7-carboxamide;  
25 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-methylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-chloroindolizine-7-carboxamide;  
30 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-bromoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylimidazo[1,2-a]pyridine-6-  
 carboxamide;  
 5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-  
 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-  
 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-  
 10 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-  
 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-methylimidazo[1,2-a]pyridine-7-  
 15 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-  
 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-  
 carboxamide;  
 20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-  
 carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-  
 carboxamide;  
 or pharmaceutically acceptable salt thereof.

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20. The compound of claim 19, wherein two R<sub>5</sub> on adjacent carbon atoms  
 combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally  
 substituted on the newly formed ring where valency allows with up to 2 substituents  
 independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl,  
 30 cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl,  
 lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl,  
 -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>,  
 -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>,

-N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,

5        wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

21.    The compound of claim 20, wherein the compound is

10    N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrido[1,2-a]indole-7-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-9H-carbazole-3-carboxamide;  
or pharmaceutically acceptable salt thereof.

22.    The compound of claim 16, wherein W<sup>1</sup> is N.

15    23.    The compound of claim 22, wherein each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

20        wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

24.    The compound of claim 23, wherein the compound is

25    N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
30    N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;



- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 10 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 15 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 20 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 25 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 30 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-
- 10 carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 15 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-
- 20 carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 25 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;
- N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;
- or pharmaceutically acceptable salt thereof.

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25. The compound of claim 22, wherein two R<sub>5</sub> on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents

independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>,  
 5 -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>,  
 -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,

10 wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

26. The compound of claim 25, wherein the compound is  
 15 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]pyrazino[1,2-a]indole-3-carboxamide;  
 N-[(exo-4S)-1-azabicyclo[2.2.1]hept-3-yl]-9H-beta-carboline-3-carboxamide;  
 or pharmaceutically acceptable salt thereof.

27. The compound of claim 4, wherein Azabicyclo is III or IV.

20 28. The compound of claim 27, wherein k is 1.

29. The compound of claim 28, wherein W<sup>1</sup> is CH.

30. The compound of claim 29, wherein each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower  
 25 halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>,  
 -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

30 31. The compound of claim 30, wherein the compound is  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]indolizine-6-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-methylindolizine-6-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-chloroindolizine-6-carboxamide;

- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-bromoindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-cyanoindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-ethynylindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylindolizine-6-carboxamide;  
5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-methylindolizine-6-carboxamide;  
10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-chloroindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-bromoindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-cyanoindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-ethynylindolizine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]indolizine-7-carboxamide;  
15 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-methylindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-chloroindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-bromoindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-1-ethynylindolizine-7-carboxamide;  
20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylindolizine-7-carboxamide;  
25 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-methylindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-chloroindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-bromoindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-3-ethynylindolizine-7-carboxamide;  
30 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;

- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;
- 5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;
- 10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;
- 15 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;
- 20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]indolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-methylindolizine-6-carboxamide;
- 25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-chloroindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-bromoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-cyanoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-ethynylindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylindolizine-6-carboxamide;
- 30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoindolizine-6-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylindolizine-6-carboxamide;

- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-methylindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-chloroindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-bromoindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-cyanoindolizine-6-carboxamide;  
5 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-ethynylindolizine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]indolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-methylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-chloroindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-bromoindolizine-7-carboxamide;  
10 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-1-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoindolizine-7-carboxamide;  
15 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-methylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-chloroindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-bromoindolizine-7-carboxamide;  
20 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylimidazo[1,2-a]pyridine-6-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoimidazo[1,2-a]pyridine-6-  
carboxamide;  
30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylimidazo[1,2-a]pyridine-6-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-a]pyridine-7-carboxamide;

- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
 5 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide; or pharmaceutically acceptable salt thereof.

- 10 32. The compound of claim 29, wherein two R<sub>5</sub> on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl,  
 15 lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam  
 20 heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,

- wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl,  
 25 or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

33. The compound of claim 32, wherein the compound is  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]pyrido[1,2-a]indole-7-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-9H-carbazole-3-carboxamide;  
 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]pyrido[1,2-a]indole-7-carboxamide;  
 30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-9H-carbazole-3-carboxamide; or pharmaceutically acceptable salt thereof.

34. The compound of claim 28, wherein W<sup>1</sup> is N.

35. The compound of claim 34, wherein each  $R_5$  is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>,  
 5 -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

36. The compound of claim 25, wherein the compound is  
 10 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 15 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-  
 20 carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;  
 25 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-  
 30 carboxamide;  
 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;



- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- 5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-
- 10 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;
- 15 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 20 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-
- 25 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 30 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-
- 10 carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;
- N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;
- 15
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- 20 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- 30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;

- N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-  
5 carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-a]pyrazine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-  
10 carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
15 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-  
20 carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
25 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-  
30 carboxamide;  
N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-  
carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;

5 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]imidazo[1,5-c]pyrimidine-7-carboxamide; or pharmaceutically acceptable salt thereof.

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37. The compound of claim 34, wherein two R<sub>5</sub> on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, 15 cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower 20 substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,

wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, 25 heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

38. The compound of claim 37, wherein the compound is

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]pyrazino[1,2-a]indole-3-carboxamide;

N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]-9H-beta-carboline-3-carboxamide;

30 N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]pyrazino[1,2-a]indole-3-carboxamide;

N-[(3R)-1-azabicyclo[3.2.1]non-3-yl]-9H-beta-carboline-3-carboxamide; or pharmaceutically acceptable salt thereof.

39. The compound of claim 4, wherein Azabicyclo is V or VI and R<sub>0</sub> is H.
40. The compound of claim 39, wherein W<sup>1</sup> is CH.
41. The compound of claim 40, wherein each R<sub>5</sub> is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,  
 wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl, and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.
42. The compound of claim 41, wherein the compound is  
 N-[2-azabicyclo[2.2.1]hept-5-yl]indolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-methylindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-chloroindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-bromoindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-cyanoindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-ethynylindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-methylindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-chloroindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-bromoindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-cyanoindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-ethynylindolizine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]indolizine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-methylindolizine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-chloroindolizine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-bromoindolizine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-cyanoindolizine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-1-ethynylindolizine-7-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoindolizine-7-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-methylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-3-cyanoindolizine-7-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-5-yl]-3-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-5-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-6-yl]indolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-chloroindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-bromoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-cyanoindolizine-6-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-6-yl]-1-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoindolizine-6-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-methylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-chloroindolizine-6-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-6-yl]-3-bromoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-cyanoindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-ethynylindolizine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]indolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-methylindolizine-7-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-6-yl]-1-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-1-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylindolizine-7-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-methylindolizine-7-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-6-yl]-3-chloroindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-bromoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-cyanoindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-3-ethynylindolizine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-a]pyridine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-6-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-bromoimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;  
 5 or pharmaceutically acceptable salt thereof.

43. The compound of claim 40, wherein two  $R_5$  on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents  
 10 independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl,  $-OR_8$ ,  $-SR_8$ ,  $-S(O)_2R_8$ ,  $-S(O)R_8$ ,  $-OS(O)_2R_8$ ,  $-N(R_8)_2$ ,  $-C(O)R_8$ ,  $-C(S)R_8$ ,  $-C(O)OR_8$ ,  $-CN$ ,  $-C(O)N(R_8)_2$ ,  $-NR_8C(O)R_8$ ,  $-S(O)_2N(R_8)_2$ ,  $-NR_8S(O)_2R_8$ ,  $-NO_2$ ,  
 15  $-N(R_8)C(O)N(R_8)_2$ , lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and  $R_{15}$ ,

- wherein each  $R_8$  is independently H, lower alkyl, lower halogenated alkyl,  
 20 lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or  $R_{15}$ .

44. The compound of claim 43, wherein the compound is  
 N-[2-azabicyclo[2.2.1]hept-5-yl]pyrido[1,2-a]indole-7-carboxamide;  
 25 N-[2-azabicyclo[2.2.1]hept-5-yl]-9H-carbazole-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]pyrido[1,2-a]indole-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-9H-carbazole-3-carboxamide; or pharmaceutically acceptable salt thereof.

- 30 45. The compound of claim 39, wherein  $W^1$  is N.

46. The compound of claim 45, wherein each  $R_5$  is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted



alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N(R<sub>10</sub>)<sub>2</sub>, -N(R<sub>10</sub>)<sub>2</sub>, -SR<sub>16</sub>, -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl, R<sub>7</sub>, or R<sub>9</sub>,

wherein each R<sub>10</sub> is independently H, lower alkyl, or lower halogenated alkyl,

5 and wherein each R<sub>16</sub> is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

47. The compound of claim 46, wherein the compound is

N-[2-azabicyclo[2.2.1]hept-5-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;

10 N-[2-azabicyclo[2.2.1]hept-5-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;

15 N-[2-azabicyclo[2.2.1]hept-5-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;

20 N-[2-azabicyclo[2.2.1]hept-5-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;

25 N-[2-azabicyclo[2.2.1]hept-5-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-a]pyrazine-6-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-a]pyrazine-6-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;

30 N-[2-azabicyclo[2.2.1]hept-5-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;

N-[2-azabicyclo[2.2.1]hept-5-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-5-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
5 N-[2-azabicyclo[2.2.1]hept-5-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
10 N-[2-azabicyclo[2.2.1]hept-5-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-5-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;  
15 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
20 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-prop-1-ynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-6-(3-hydroxyprop-1-ynyl)pyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
25 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
30 N-[2-azabicyclo[2.2.1]hept-6-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-carboxamide;  
N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-a]pyrazine-6-carboxamide;

- N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-a]pyrazine-6-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 5 N-[2-azabicyclo[2.2.1]hept-6-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 10 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 15 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]imidazo[1,5-c]pyrimidine-7-carboxamide; or  
 20 pharmaceutically acceptable salt thereof.

48. The compound of claim 45, wherein two R<sub>5</sub> on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents  
 25 independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>,  
 30 -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,

wherein each  $R_8$  is independently H, lower alkyl, lower halogenated alkyl, lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or  $R_{15}$ .

- 5 49. The compound of claim 48, wherein the compound is  
 N-[2-azabicyclo[2.2.1]hept-5-yl]pyrazino[1,2-a]indole-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-5-yl]-9H-beta-carboline-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]pyrazino[1,2-a]indole-3-carboxamide;  
 N-[2-azabicyclo[2.2.1]hept-6-yl]-9H-beta-carboline-3-carboxamide; or  
 10 pharmaceutically acceptable salt thereof.

50. The compound of claim 4, wherein Azabicyclo is VII.

51. The compound of claim 50, wherein each  $R_3$  is independently H, lower alkyl, or lower substituted alkyl.

- 15 52. The compound of claim 51, wherein  $R_4$  is H, lower alkyl optionally substituted with up to 3 substituents independently selected from F, Cl, Br, I, -OH, -CN, -NH<sub>2</sub>, -NH(lower alkyl), or -N(lower alkyl)<sub>2</sub>.

53. The compound of claim 52, wherein  $R_4$  is an amino protecting group.

54. The compound of claim 52, wherein each  $R_3$ , and  $R_4$  are H.

- 20 55. The compound of claim 54, wherein  $W^1$  is CH.

56. The compound of claim 55, wherein each  $R_5$  is independently H, lower alkyl, lower substituted alkyl, lower halogenated alkyl, lower alkenyl, lower substituted alkenyl, lower halogenated alkenyl, lower alkynyl, lower substituted alkynyl, lower halogenated alkynyl, -CN, -NO<sub>2</sub>, F, Br, Cl, I, -OR<sub>16</sub>, -C(O)N( $R_{10}$ )<sub>2</sub>, -N( $R_{10}$ )<sub>2</sub>, -SR<sub>16</sub>,  
 25 -S(O)<sub>2</sub>R<sub>16</sub>, -C(O)R<sub>16</sub>, -CO<sub>2</sub>R<sub>16</sub>, phenyl, substituted phenyl,  $R_7$ , or  $R_9$ ,

wherein each  $R_{10}$  is independently H, lower alkyl, or lower halogenated alkyl, and wherein each  $R_{16}$  is independently H, lower alkyl, lower halogenated alkyl, or lower substituted alkyl.

57. The compound of claim 56, wherein the compound is  
 30 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]indolizine-6-carboxamide;  
 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-methylindolizine-6-carboxamide;  
 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-chloroindolizine-6-carboxamide;  
 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-bromoindolizine-6-carboxamide;

- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-cyanoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-ethynylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroindolizine-6-carboxamide;  
5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-methylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-chloroindolizine-6-carboxamide;  
10 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-bromoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-cyanoindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-ethynylindolizine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]indolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-methylindolizine-7-carboxamide;  
15 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-chloroindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-bromoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-cyanoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-1-ethynylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylindolizine-7-carboxamide;  
20 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-methylindolizine-7-carboxamide;  
25 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-chloroindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-bromoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-cyanoindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-3-ethynylindolizine-7-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-a]pyridine-7-carboxamide;  
30 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-a]pyridine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-a]pyridine-6-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;

- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroimidazo[1,2-a]pyridine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoimidazo[1,2-a]pyridine-6-carboxamide;
- 5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoimidazo[1,2-a]pyridine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylimidazo[1,2-a]pyridine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-a]pyridine-7-carboxamide;
- 10 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-methylimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-chloroimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-bromoimidazo[1,2-a]pyridine-7-
- 15 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-cyanoimidazo[1,2-a]pyridine-7-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-2-ethynylimidazo[1,2-a]pyridine-7-carboxamide;
- 20 or pharmaceutically acceptable salt thereof.

58. The compound of claim 55, wherein two R<sub>5</sub> on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl,
- 25 cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>, -CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>, -N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower
- 30 substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents independently selected from F, Cl, Br, I and R<sub>15</sub>,



- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-ethynylpyrrolo[1,2-a]pyrazine-3-
- 10 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-cyanopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-methylpyrrolo[1,2-a]pyrazine-3-carboxamide;
- 15 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-chloropyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-bromopyrrolo[1,2-a]pyrazine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-8-ethynylpyrrolo[1,2-a]pyrazine-3-
- 20 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-a]pyrazine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-a]pyrazine-6-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-pyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 25 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-chloropyrrolo[1,2-c]pyrimidine-3-
- 30 carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;



- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-5-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 5 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 10 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-6-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-cyanopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 15 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-methylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-chloropyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-bromopyrrolo[1,2-c]pyrimidine-3-carboxamide;
- 20 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-7-ethynylpyrrolo[1,2-c]pyrimidine-3-carboxamide;
- N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,2-c]pyrimidine-7-carboxamide;
- 25 N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]imidazo[1,5-c]pyrimidine-7-carboxamide;

63. The compound of claim 60, wherein two R<sub>5</sub> on adjacent carbon atoms combine for W to be the 6-5-6 fused-tricyclic-heteroaromatic-ring system optionally substituted on the newly formed ring where valency allows with up to 2 substituents
- 30 independently selected from F, Cl, Br, I, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, lower halogenated alkyl, lower halogenated alkenyl, lower halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR<sub>8</sub>, -SR<sub>8</sub>, -S(O)<sub>2</sub>R<sub>8</sub>, -S(O)R<sub>8</sub>, -OS(O)<sub>2</sub>R<sub>8</sub>, -N(R<sub>8</sub>)<sub>2</sub>, -C(O)R<sub>8</sub>, -C(S)R<sub>8</sub>, -C(O)OR<sub>8</sub>,

- CN, -C(O)N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>C(O)R<sub>8</sub>, -S(O)<sub>2</sub>N(R<sub>8</sub>)<sub>2</sub>, -NR<sub>8</sub>S(O)<sub>2</sub>R<sub>8</sub>, -NO<sub>2</sub>,  
-N(R<sub>8</sub>)C(O)N(R<sub>8</sub>)<sub>2</sub>, lower substituted alkyl, lower substituted alkenyl, lower  
substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam  
heterocycloalkyl, or phenyl optionally substituted with up to 2 substituents  
5 independently selected from F, Cl, Br, I and R<sub>15</sub>,

wherein each R<sub>8</sub> is independently H, lower alkyl, lower halogenated alkyl,  
lower substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl,  
heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl,  
or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R<sub>15</sub>.

- 10 64. The compound of claim 63, wherein the compound is  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]pyrazino[1,2-a]indole-3-carboxamide;  
N-[(1S,2R,4R)-7-azabicyclo[2.2.1]hept-2-yl]-9H-beta-carboline-3-carboxamide;  
or pharmaceutically acceptable salt thereof.
65. A pharmaceutical composition comprising a compound according to any one  
15 of claims 1-64, anti-psychotic agent(s), and a pharmaceutically acceptable excipient.
66. The pharmaceutical composition according to claim 65, wherein said  
compound and said agent are to be independently administered rectally, topically,  
orally, sublingually, or parenterally for a therapeutically effective interval.
67. The pharmaceutical composition according to claim 66, wherein said  
20 compound is administered in an amount of from about 0.001 to about 100 mg/kg of  
body weight of said mammal per day.
68. The pharmaceutical composition according to claim 66, wherein said  
compound is administered in an amount of from about 0.1 to about 50 mg/kg of body  
weight of said mammal per day.
- 25 69. The pharmaceutical composition according to claim 65, comprising a  
compound according to any one of claims 1-64 and a pharmaceutically acceptable  
excipient.
70. The pharmaceutical composition according to claim 69, wherein said  
compound is administered rectally, topically, orally, sublingually, or parenterally for a  
30 therapeutically effective interval.
71. The pharmaceutical composition according to claim 70, wherein said  
compound is administered in an amount of from about 0.001 to about 100 mg/kg of  
body weight of said mammal per day.

72. The pharmaceutical composition according to claim 70, wherein said compound is administered in an amount of from about 0.1 to about 50 mg/kg of body weight of said mammal per day.
- 5 73. Use of a compound according to any one of claims 1-64 for the preparation of a medicament for treating a disease or condition, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of  $\alpha 7$  nicotinic acetylcholine receptor agonist.
- 10 74. The use according to claim 73, wherein the disease or condition is cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), or senile dementia.
- 15 75. The use according to claim 73, wherein the disease or condition is schizophrenia or psychosis.
76. The use of claim 75, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of  $\alpha 7$  nicotinic acetylcholine receptor agonist and an anti-psychotic agent for a therapeutically
- 20 effective interval.
77. The use according to claim 73, wherein the disease or condition is depression, anxiety, general anxiety disorders, or post traumatic stress disorder.
- 25 78. The use according to claim 73, wherein the disease or condition is attention deficit disorder, or attention deficit hyperactivity disorder.
79. The use according to claim 73, wherein the disease or condition is mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder,
- 30 traumatic brain injury, behavioral and cognitive problems in general and associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including

bulemia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

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80. A method for treating a disease or condition in a mammal in need thereof, wherein the mammal would receive symptomatic relief from the administration of an  $\alpha 7$  nicotinic acetylcholine receptor agonist comprising administering to the mammal a therapeutically effective amount of a compound according to any one of claims 1-64.

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81. The method according to claim 80, wherein the disease or condition is cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), or senile dementia.

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82. The method according to claim 80, wherein the disease or condition is schizophrenia or psychosis.

83. The method of claim 82, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of  $\alpha 7$  nicotinic acetylcholine receptor agonist and an anti-psychotic agent for a therapeutically effective interval.

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84. The method according to claim 80, wherein the disease or condition is depression, or anxiety and general anxiety disorders and post traumatic stress disorder.

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85. The method according to claim 80, wherein the disease or condition is attention deficit disorder, or attention deficit hyperactivity disorder.

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86. The method according to claim 80, wherein the disease or condition is mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems in general and associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's

disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including  
bulemia and anorexia nervosa, withdrawal symptoms associated with smoking  
cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related  
macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or  
5 symptoms associated with pain.

## INTERNATIONAL SEARCH REPORT

Inter Application No  
PCT/US 03/02687A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D519/00 A61K31/439 A61K31/4985 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 36417 A (ASTRAZENECA) 25 May 2001 (2001-05-25) page 17, line 17 -page 18, line 12; claims; examples	1-86
Y	WO 01 29034 A (ASTRAZENECA) 26 April 2001 (2001-04-26) page 10, line 18 -page 11, line 13; claims; examples	1-86
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

25 June 2003

Date of mailing of the international search report

03/07/2003

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## INTERNATIONAL SEARCH REPORT

Inter al Application No

PCT/US 03/02687

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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P,Y	WO 02 100858 A (PHARMACIA AND UPJOHN) 19 December 2002 (2002-12-19) page 30, line 19 -page 41, line 28; claims; examples	1-86
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

In .....tional application No.  
PCT/US 03/02687

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 80 to 86 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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